ICH S1B(R1): US REGULATORY PERSPECTIVES ON THE NEW WEIGHT OF EVIDENCE APPROACH

MAY 3, 2023

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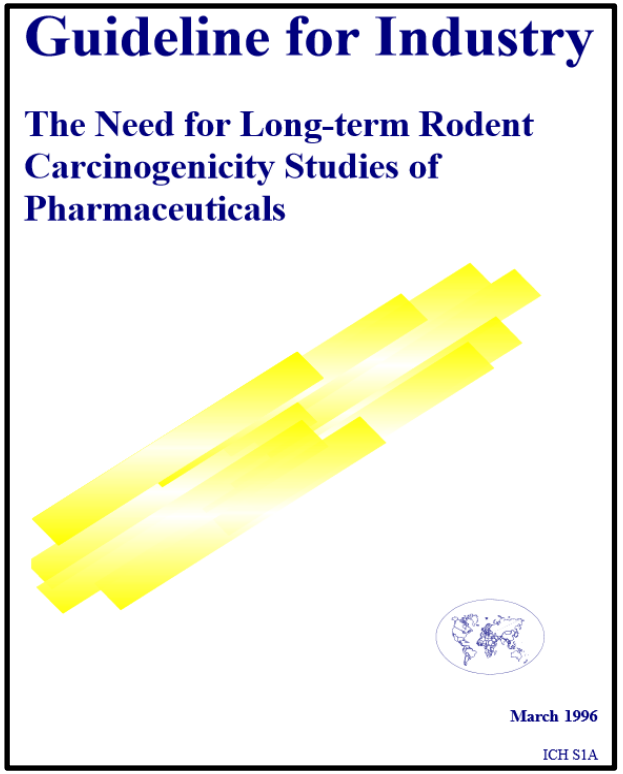
Outline

- Describe the key aspects of the new ICH S1B(R1) Addendum
- Describe FDA's current process for evaluation of WoE submissions
- Discuss FDA's experience with WoE evaluations

Regulatory Framework for Carcinogenicity Assessment of Pharmaceuticals: 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



ICH S1B: Testing for Carcinogenicity of Pharmaceuticals

Purpose of the ICH S1B guidance

- Guidance on approaches for evaluating carcinogenic potential of pharmaceuticals

Document history

- July 1997: Original guideline adopted by ICH
- 2011: Expert Working Group (EWG) convened to discuss Addendum
- August 2022: ICH S1B(R1) Addendum finalized by ICH
- November 2022: FDA Guidance for Industry ICH S1B(R1) published in US Federal Register

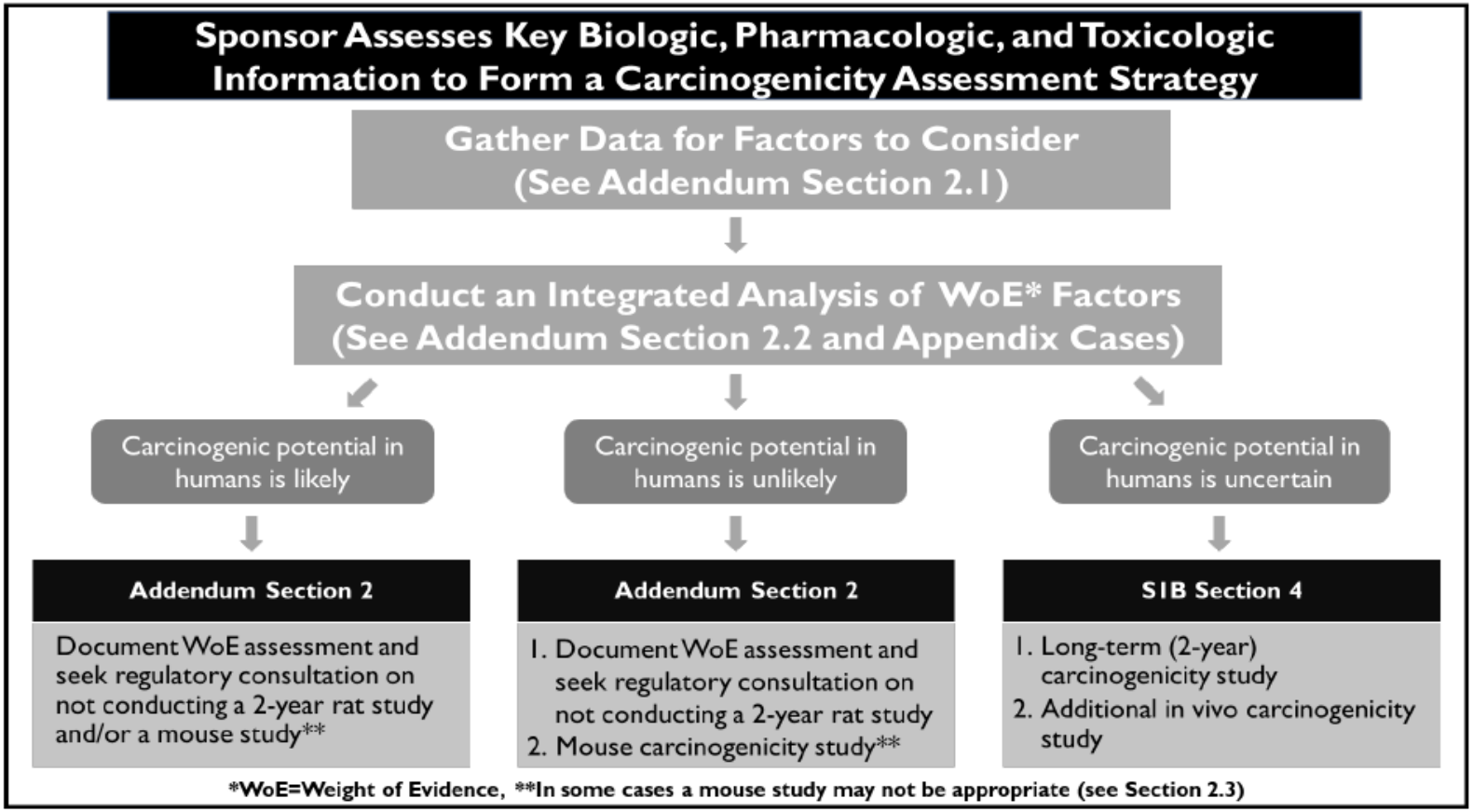
ICH S1B(R1): Carcinogenicity Testing - Addendum

Purpose of the Addendum

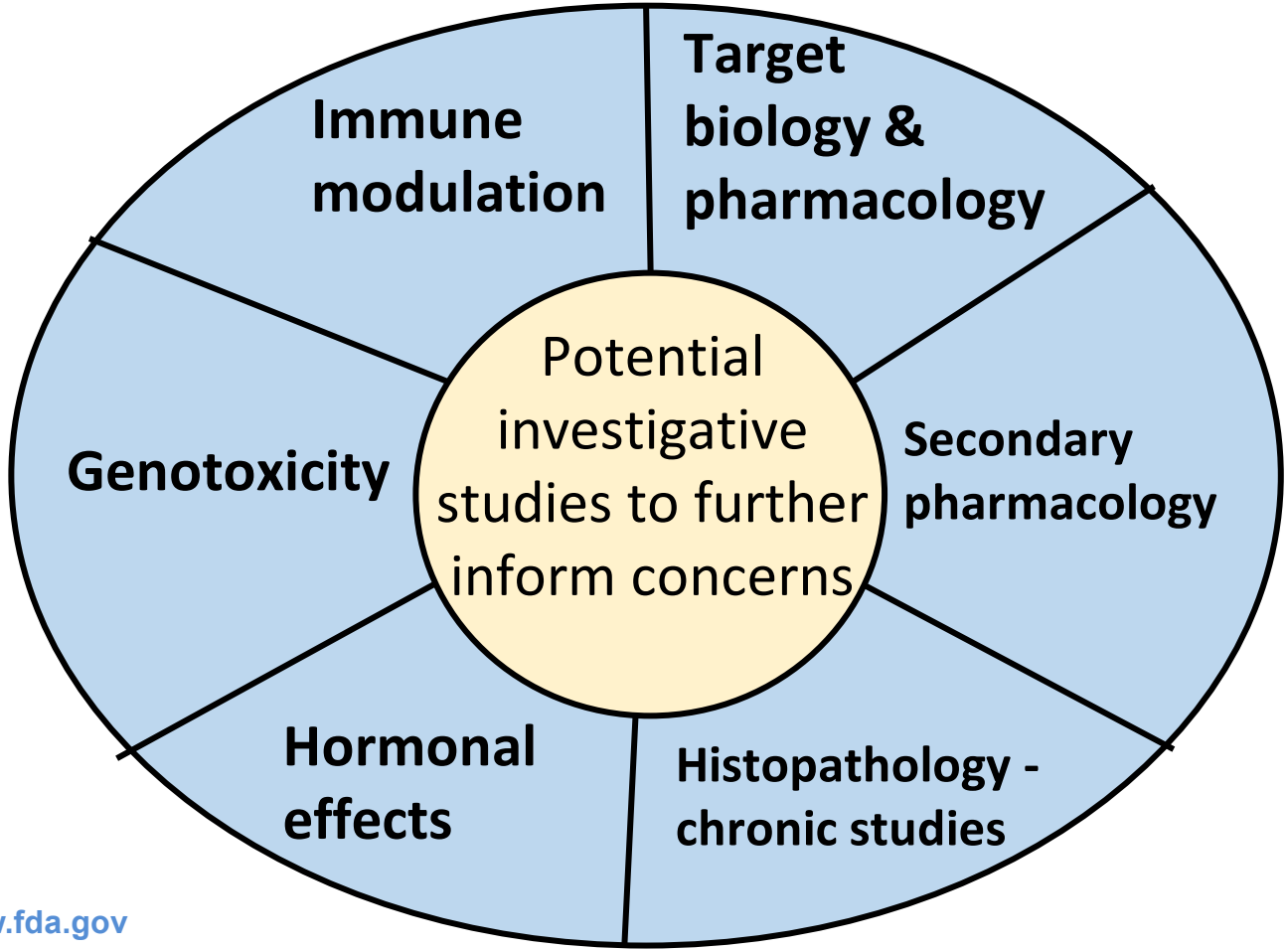
- Expands the evaluation process for assessing human carcinogenic risk of pharmaceuticals
  - Weight-of-evidence (WoE) approach to determine if a 2-year rat study adds value
  - Does not replace existing S1B guidance; to be used in conjunction with the S1A-C guidances

- Includes a plasma exposure ratio endpoint (50X human exposure) for high-dose selection in rasH2-Tg mouse model

ICH S1B(R1) Flow Scheme - Carcinogenicity Assessment Strategy



ICH S1B(R1) - Weight of Evidence Factors



WoE Factors: Target Biology & Pharmacology

- Drug target biology
- Primary pharmacologic mechanism (parent & major human metabolites)
  - Drug target distribution in rats and humans
  - Pharmacologic activity in rats and humans
- Carcinogenicity data from class
- Genetically engineered models
- Human genetic association studies
- Cancer gene databases

WoE Factors: Secondary Pharmacology

- Secondary pharmacology screen(s) that inform
  - Selectivity
  - Off-target potential
  - Carcinogenic risk (e.g., binding to nuclear receptors)

- Conducted for parent compound & major human metabolites

WoE Factors: Histopathology - Chronic Studies

- Primary source of histopathology data
  - 6-month rat study
- Potential additional sources of histopathology data
  - Shorter-term rat studies
  - Longer-term non-rodent studies
  - Longer-term mouse studies

WoE Factors: Histopathology - Chronic Studies

- Treatment-related findings of particular importance
  - Cellular hypertrophy
  - Cellular hyperplasia
  - Persistent tissue injury and/or chronic inflammation
  - Pre-neoplastic changes
  - Tumors

Important to understand pathogenesis
& likely human relevance
(e.g., mechanism, plasma exposure margins)

WoE Factors: Hormonal Effects

- Knowledge of drug target and pharmacologic mechanisms
  - Examples: hormone receptor binding, regulation of hormone levels
- Knowledge of potential compensatory response mechanisms
- Relevant data from reproductive toxicology studies

WoE Factors: Hormonal Effects

- Alterations in endocrine & reproductive organs from rat repeat-dose toxicity studies

- Treatment-related findings of particular importance
  - Biologically significant changes in organ weights
  - Atrophy
  - Hypertrophy
  - Hyperplasia

Important to understand pathogenesis
& likely human relevance
(e.g., mechanism, plasma exposure margins)

WoE Factors

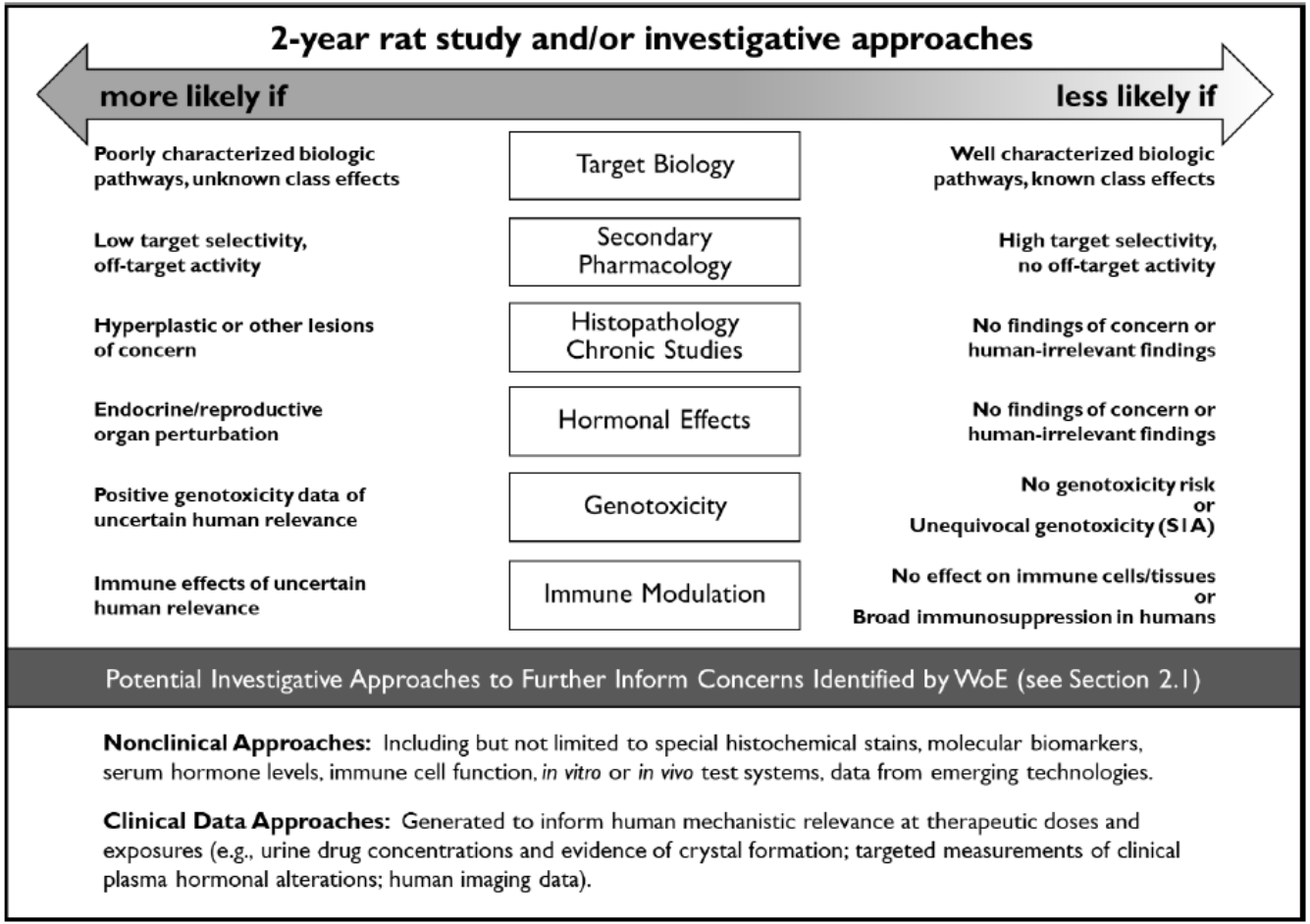
Genotoxicity

Data from studies recommended in ICH S2 guideline

Immune Modulation

Data from studies recommended in ICH S8 guideline

ICH S1B(R1) – Integration of WoE factors



Mouse Carcinogenicity Studies

Remains recommended component of the carcinogenicity testing plan

- Consists of either:
  - Two-year study in standard strain
  - Short-term study in transgenic model

- Unless there is scientific rationale for conducting 2-year mouse study, should prioritize use of transgenic model

Mouse Carcinogenicity Studies

May not be warranted in cases where WoE indicates:

- Compound likely carcinogenic in humans
- No carcinogenic risk to humans and subtherapeutic, pharmacologically inactive drug levels achieved in mice (compared with human exposure)

WoE Procedures - Sponsors

- Conduct WoE assessment based on all factors described in the S1B(R1) Addendum
- Does assessment support conclusion that a 2-yr rat study would not add value to the assessment of human carcinogenicity risk?
    - Submit WoE assessment to relevant application (presumably an IND) with a request that the assessment be accepted in lieu of a 2-yr rat study.

Notes:

- Acceptance of a WoE assessment is not considered a “waiver” by regulatory definition.
- Fully address any potential findings of concern and/or lack of human relevance to allow for a more efficient regulatory review.

WoE Procedures - FDA Office of New Drugs

Review process is similar to that for a carcinogenicity Special Protocol Assessment (SPA):

- Review Division evaluates sponsor submission & presents sponsor's rationale and Division's recommendation
- Executive Carcinogenicity Assessment Committee (ECAC) & Pharm/Tox Division Directors provide feedback to the review Division
- Review Division then communicates agreement/disagreement with sponsor's proposal with any relevant comments

WoE Procedures – FDA/Office of New Drugs

2 key differences from the SPA process:

- No minutes of the review meeting are provided to the sponsor
- No formal review clock as submissions are not associated with any user fee goal dates
  - FDA is evaluating submissions as quickly as current workloads allow

FDA Experience to Date

- Limited number of submissions evaluated so far
- Overall rate of agreement with sponsors' proposals will be clearer over time
  - In S1B EWG prospective study, DRAs agreed with sponsor proposals that a 2-year rat study did not add value to human risk assessment for approximately 25% of CAD submissions
- FDA plans to periodically compare our experience with other DRAs with the goal of enhancing consistency in approach globally
- DRAs also drafting a publication a detailed evaluation of the prospective study – planned publication in 2023.

Acknowledgements

- Todd Bourcier, PhD, OND/CDER/FDA
- Alisa Vespa, PhD, Health Canada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U.S. FOOD & DRUG
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