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# Updates on ICH Safety-Related Guidelines: ICH M7(R2) & ICH S1B(R1) Addendum

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# Presentation Outline

- M7(R2): Assessment and Control of DNA Reactive (mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

- S1B(R1): Testing for Carcinogenicity of Pharmaceuticals

# ICH M7(R1): Mutagenic impurities

## Purpose & history of M7 guideline

- Main guideline
  - Provide guidance and a framework for the assessment and control of mutagenic impurities in pharmaceuticals
  - Adopted by ICH in June 2014
- Addendum
  - Monographs and acceptable limits for 14 compounds
  - Adopted by ICH in May 2017

# ICH M7(R2): Mutagenic impurities

## Scope of current update

- Main guideline
- Addendum
  - Monographs and acceptable limits for seven (7) additional compounds
- Questions and Answers (Q&A) document

# ICH M7(R2): Change to the main guideline

Note 7:

| Scenario[1] | Acceptable Intake (µg/day) |
|---|---|
| **Treatment duration of ≤ 1 month**: e.g., drugs used in emergency procedures (antidotes, anesthesia, acute ischemic stroke), actinic keratosis, treatment of lice | 120 |
| **Treatment duration of > 1-12 months:** e.g., anti-infective therapy with maximum up to 12 months treatment (HCV), parenteral nutrients, prophylactic flu drugs (~ 5 months), peptic ulcer, Assisted Reproductive Technology (ART), pre-term labor, preeclampsia, pre-surgical (hysterectomy) treatment, fracture healing (these are acute use but with long half-lives) | 20 |
| **Treatment duration of >1-10 years:** e.g., stage of disease with short life expectancy (severe Alzheimer's), non-genotoxic anticancer treatment being used in a patient population with longer term survival (breast cancer, chronic myelogenous leukemia), drugs specifically labeled for less than 10 years of use, drugs administered intermittently to treat acute recurring symptoms[2] (chronic Herpes, gout attacks, substance dependence such as smoking cessation), macular degeneration~~, HIV~~[3] | 10 |
| **Treatment duration of >10 years to lifetime:** e.g., chronic use indications with high likelihood for lifetime use across broader age range (hypertension, dyslipidemia, asthma, Alzheimer's (except severe Alzheimer disease), hormone therapy (e.g., growth hormone, thyroid hormone, parathyroid hormone), lipodystrophy, schizophrenia, depression, psoriasis, atopic dermatitis, Chronic Obstructive Pulmonary Disease (COPD), cystic fibrosis, seasonal and perennial allergic rhinitis, HIV[3] | 1.5 |

# ICH M7(R2): Addendum – mutagenic/carcinogenic impurities to be added

| Impurity | Final limit |
|---|---|
| 1,2-Dibromoethane | 2 µg/day |
| Epichlorohydrin | 3 µg/day |
| Ethyl bromide | 32 µg/day |
| Formaldehyde | 8 mg/day or 215 ppb, whichever is lower (inhalation)<br>10 mg/day (all other routes) |
| Styrene | 154 µg/day |
| Acetaldehyde | 2 mg/day (oral)<br>185 µg/day (all other routes) |
| Vinyl acetate | 2 mg/day (oral)<br>185 µg/day (all other routes) |

# ICH M7(R2): Addendum

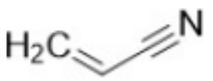
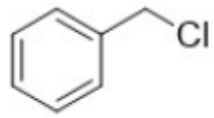
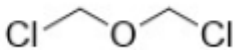
## Outcome of regulatory consultation

- No changes to any of the proposed Step 1 limits
- Mainly editorial changes to provide more clarity and consistency
- Note 3 added to the formaldehyde monograph
  - Sample calculation of acceptable concentration limit when formaldehyde present as an impurity in the API or drug product (inhalation route)

# ICH M7(R2): Addendum

- Addendum to be placed in a separate document from ICH M7 main guideline

- Appendix 3 of main guideline will contain summary table (excerpt below)

| Compound | CAS# | Chemical Structure | AI or PDE (µg/day) | Comment |
|---|---|---|---|---|
| **Linear extrapolation from $TD_{50}$** | | | | |
| Acrylonitrile | 107-13-1 |  | 6 | $TD_{50}$ linear extrapolation |
| Benzyl chloride | 100-44-7 |  | 41 | $TD_{50}$ linear extrapolation |
| Bis(chloromethyl)ether | 542-88-1 |  | 0.004 | $TD_{50}$ linear extrapolation |

# ICH M7(R2): Questions and Answers document

## Objective of the Q&A

- Clarify details in the guideline which were unclear or led to different interpretation by stakeholders

- Facilitate harmonization and implementation of ICH M7 recommendations

# ICH M7(R2): Questions and Answers document

## Work process

- Stakeholders submitted more than 100 questions
- Expert working group consolidated related questions
- A total of 25 Q&As will be included in the final document

# ICH M7(R2): Questions and Answers document

## Table of contents

- Q&A document structured in the same manner as the M7 guideline
  - Section 1 Introduction: 4 Q&As
  - Section 2 Scope: 1 Q&A
  - Section 3 General Principles: 2 Q&As
  - Section 4 Marketed products: 1 Q&A
  - Section 5 Drug substance/drug product impurity assessment: None
  - Section 6 Hazard assessment: 4 Q&As
  - Section 7 Risk characterization: 5 Q&As
  - Section 8 Control: 6 Q&As
  - Section 9 Documentation: 2 Q&As

# ICH M7(R2): Questions and Answers document

## Outcome of regulatory consultation

- No changes to the recommendations
- Mainly editorial changes to provide more clarity

# ICH M7(R2): Main guideline, Addendum, Q&A

## Next steps

- Currently in Step 3 (regulatory consultation, EWG discussion, document revision)

- Finalization as a Step 4 document expected in the near future

# ICH S1B(R1):

# Guideline on Testing for Carcinogenicity of Pharmaceuticals

# ICH S1B(R1): Carcinogenicity Testing

## Purpose of the ICH S1B guideline

- Guidance on approaches for evaluating the carcinogenic potential of pharmaceuticals

## Document history

- ICH S1B guideline adopted by ICH in July 1997

# ICH S1B(R1): Carcinogenicity Testing

## Options for carcinogenicity testing

Option 1

- 2-year study in one rodent species (e.g., rat)
- Short- or medium-term *in vivo* rodent study (e.g., RasH2-Tg)

Option 2

- 2-year study in one rodent species (rat)
- 2-year study in 2$^{nd}$ rodent species (mouse)

# ICH S1B(R1): Carcinogenicity Testing - Addendum

## Work process and timeline

- Concept paper and business plan developed (November 2012)
- Prospective evaluation study launched (August 2013)
  - Regulatory Notice Document (RND) posted on ICH website
  - Several status reports posted on ICH website
- Step 1 draft Addendum endorsed by ICH Assembly (April 2021)
- Step 3 regulatory consultation, EWG discussion, document revision (July 2022)
- Step 4 adoption of guideline by ICH Assembly (August 2022)

https://database.ich.org/sites/default/files/S1B-R1_FinalGuideline_2022_0719.pdf

# ICH S1B(R1): Carcinogenicity Testing - Addendum

## Purpose of the Addendum

- Expands the options for assessing human carcinogenic risk of pharmaceuticals
  - Weight of Evidence (WoE) approach to determine if 2-year rat study adds value
  - Does not replace existing S1B guideline
  - Scope does not include biotechnology derived pharmaceuticals

- Includes a plasma exposure ratio endpoint for high-dose selection in rasH2-Tg mouse model

# ICH S1B(R1): Carcinogenicity Testing - Addendum

## Possible conclusions following WoE assessment (section 2.)

- Likely to be carcinogenic in humans
- Likely not to be carcinogenic in humans

} 2-year rat study will not add value

- Carcinogenic potential in humans uncertain

} 2-year rat study will add value

# ICH S1B(R1): Carcinogenicity Testing - Addendum

## Factors to consider in the WoE assessment (section 2.1)

- Drug target biology & primary pharmacologic mechanism
  - Carcinogenicity data for compounds in drug class
- Secondary pharmacology (off-target potential)
- Histopathology data from repeat-dose toxicity studies
  - 6-month rat study most informative
- Hormonal perturbation
- Genotoxicity (ICH S2)
- Immune modulation (ICH S8)

# ICH S1B(R1): Carcinogenicity Testing - Addendum

## If WoE factor(s) inconclusive or indicate a concern (section 2.1)

- Investigative studies may further inform human relevance of potential risk
  - Non-clinical approaches (e.g., histochemical stains)
  - Clinical approaches (e.g., plasma hormone levels)

# ICH S1B(R1): Carcinogenicity Testing - Addendum

## Integration of WoE factors (section 2.2)

- Integrated analysis informs if 2-year rat study will add value to assessment of human carcinogenic risk
  - Case studies in Appendix to Addendum

# ICH S1B(R1): Carcinogenicity Testing - Addendum

## Mouse carcinogenicity studies (section 2.3)

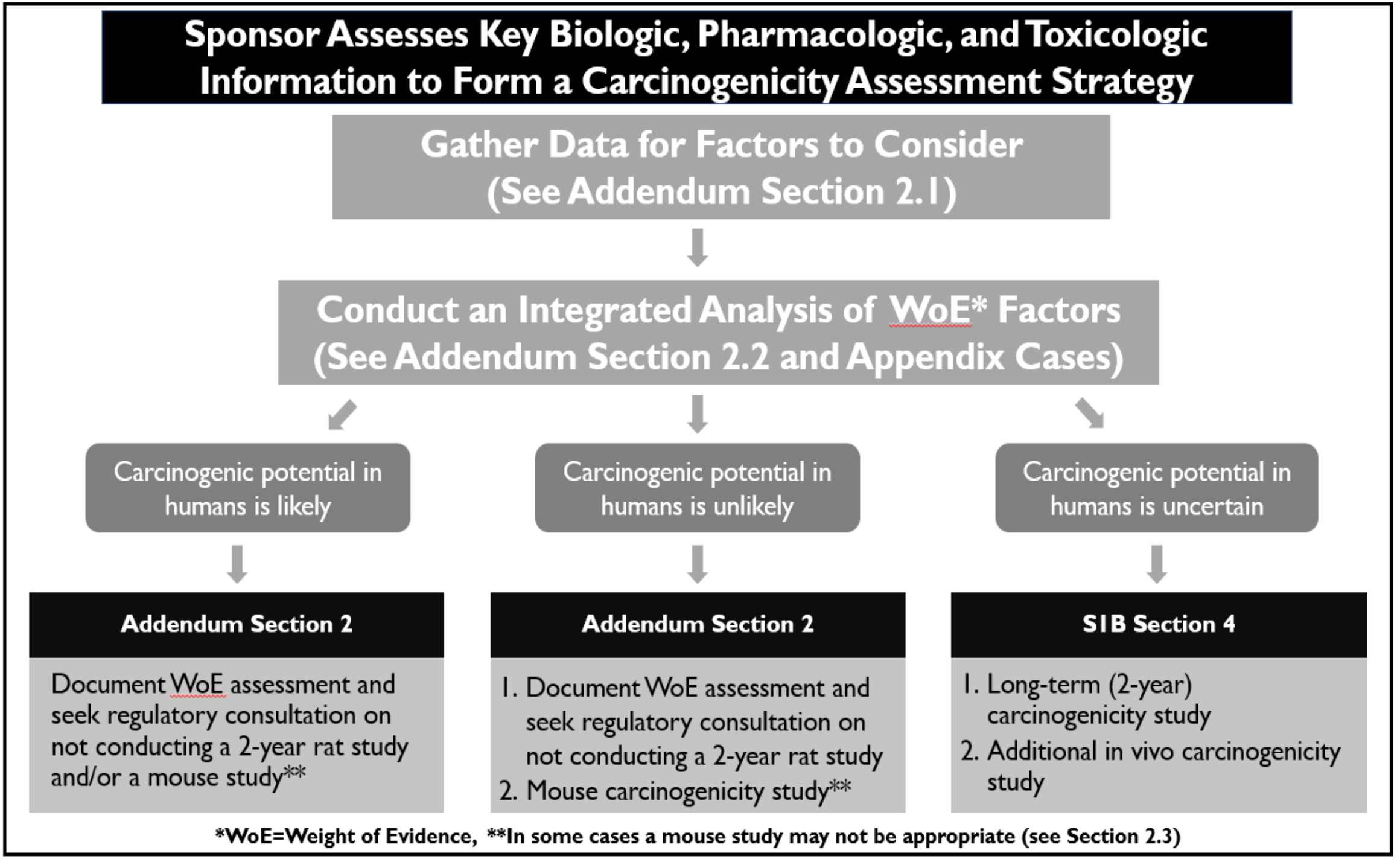
- Remains recommended component of carcinogenicity testing plan

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

# ICH S1B(R1): Carcinogenicity Testing - Addendum

## Outcome of Step 3 regulatory consultation

- No substantial changes to recommendations
  - Several editorial changes made to improve flow and provide clarity
- Two figures added to visually represent how the WoE approach is carried out


Sponsor Assesses Key Biologic, Pharmacologic, and Toxicologic Information to Form a Carcinogenicity Assessment Strategy
Gather Data for Factors to Consider (See Addendum Section 2.1)
Conduct an Integrated Analysis of WoE* Factors (See Addendum Section 2.2 and Appendix Cases)
Carcinogenic potential in humans is likely
Carcinogenic potential in humans is unlikely
Carcinogenic potential in humans is uncertain
Addendum Section 2
Document WoE assessment and seek regulatory consultation on not conducting a 2-year rat study and/or a mouse study**
Addendum Section 2
1. Document WoE assessment and seek regulatory consultation on not conducting a 2-year rat study
2. Mouse carcinogenicity study**
S1B Section 4
1. Long-term (2-year) carcinogenicity study
2. Additional in vivo carcinogenicity study
*WoE=Weight of Evidence, **In some cases a mouse study may not be appropriate (see Section 2.3)

## 2-year rat study and/or investigative approaches

| more likely if | | less likely if |
|---|---|---|
| **Poorly characterized biologic pathways, unknown class effects** | Target Biology | **Well characterized biologic pathways, known class effects** |
| **Low target selectivity, off-target activity** | Secondary Pharmacology | **High target selectivity, no off-target activity** |
| **Hyperplastic or other lesions of concern** | Histopathology Chronic Studies | **No findings of concern or human-irrelevant findings** |
| **Endocrine/reproductive organ perturbation** | Hormonal Effects | **No findings of concern or human-irrelevant findings** |
| **Positive genotoxicity data of uncertain human relevance** | Genotoxicity | **No genotoxicity risk or Unequivocal genotoxicity (S1A)** |
| **Immune effects of uncertain human relevance** | Immune Modulation | **No effect on immune cells/tissues or Broad immunosuppression in humans** |

### Potential Investigative Approaches to Further Inform Concerns Identified by WoE (see Section 2.1)

**Nonclinical Approaches:** Including but not limited to special histochemical stains, molecular biomarkers, serum hormone levels, immune cell function, *in vitro* or *in vivo* test systems, data from emerging technologies.

**Clinical Data Approaches:** Generated to inform human mechanistic relevance at therapeutic doses and exposures (e.g., urine drug concentrations and evidence of crystal formation; targeted measurements of clinical plasma hormonal alterations; human imaging data).

# ICH S1B(R1): Carcinogenicity Testing - Addendum

## Outcome of Step 3 regulatory consultation

- New recommendation in section 2.3 (mouse carcinogenicity studies):

"Use of a transgenic model is consistent with the 3R (reduce/refine/replace) principles and this model should be prioritized unless there is a scientific rationale for conducting a 2-year study in mice."

# Acknowledgements


- ICH M7 expert working group
- ICH S1 expert working group