SBIA-DMF and Drug Substance Workshop
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ICH M7(R1) – CHEMISTRY AND MANUFACTURING CONTROL (CMC) PERSPECTIVE ON IMPURITY HAZARD ASSESSMENT

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Outline

- ICH M7 background
- ICH M7 scope and key concepts
- Review of hazard assessment steps and how it is used to classify impurities
- Example hazard assessment and how it is evaluated by the Agency
- Sample calculation: impact of indication, treatment duration, and dose
- Analytical method considerations

Background

- **ICH M7:** ASSESSMENT AND CONTROL OF DNA REACTIVE (MUTAGENIC) IMPURITIES IN PHARMACEUTICALS TO LIMIT POTENTIAL CARCINOGENIC RISK
  - Step 4 June 2014
- **Addendum**
  - Step 4 March 2017
- **ICH M7 Questions and Answers**
  - Supporting document which provides clarification on both safety and chemistry aspects of the guideline
  - Step 2b as of June 2020; public comment phase completed and questions being addressed by ICH Expert Working Group

What Drug Substances/Products are Out of Scope for M7?

Refer to Section 2 of the Guidance and ICH M7 Q&A *(Step 2)* #s 2.1, 4.1, 6.3

- Biological/biotechnological, peptides, oligonucleotides, radiopharmaceutical, fermentation, herbal, crude products of animal or plant origin
- Drugs intended to be used for **advanced** cancer
- API's that are genotoxic at therapeutic concentrations
- Already approved products unless there are:
  - Changes to the DS synthesis resulting in new impurities or increased acceptance criteria for existing impurities
  - Changes in the formulation, composition or manufacturing process result in new degradation products or increased acceptance criteria for existing degradation products
  - Changes in indication or dosing regimen are made which significantly affect the acceptable cancer risk level.

CMC Impurity Assessment

A collaborative approach is used and requires both CMC and Safety expertise

- Impurities identified in DS/DP
- Starting materials; reagents
- Identified impurities in starting materials
- Synthetic intermediates
- Reasonably expected by-products and degradants

- Assess Risk (Q)SAR / Ames
- Customize TTC (if appropriate)
- Input on Control Strategy

The Hazard Assessment: What is it?

Per ICH M7, Section 6:

> **6. HAZARD ASSESSMENT ELEMENTS**
>
> Hazard assessment involves an initial analysis of actual and potential impurities by conducting database and literature searches for carcinogenicity and bacterial mutagenicity data in order to classify them as Class 1, 2, or 5 according to Table 1. If data for such a classification are not available, an assessment of Structure-Activity Relationships (SAR) that focuses on bacterial mutagenicity predictions should be performed. This could lead to a classification into Class 3, 4, or 5.

Translation to Industry: If literature or Ames data cannot be found for the starting material, intermediates, or organic impurities, then run (Q)SAR (endpoint Mutagenicity/DNA reactivity) to "bucket" the compounds appropriately according to Table 1.

NOTE: ***Visual inspection*** *of a compound for structural alerts for classification purposes is* ***not*** *M7 compliance.*

ICH M7 Section 6: Impurity Classes

Table 1: Impurities Classification with Respect to Mutagenic and Carcinogenic Potential and Resulting Control Actions (according to Ref. 17 with modifications)

Class	Definition	Proposed action for control (details in Section 7)
1	Known mutagenic carcinogens	Control at or below compound-specific acceptable limit
2	Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive*, no rodent carcinogenicity data)	Control at or below acceptable limits (generic or adjusted TTC)
3	Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data.	Control at or below acceptable limits (generic or adjusted TTC) or do bacterial mutagenicity assay; If non-mutagenic = Class 5 If mutagenic = Class 2
4	Alerting structure, same alert in drug substance which has been tested and is non-mutagenic	Treat as non-mutagenic impurity
5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity	Treat as non-mutagenic impurity

Mutagenic

Non-mutagenic

*Or other relevant positive mutagenicity data indicative of DNA-reactivity related induction of gene mutations (e.g., positive findings in *in vivo* gene mutation studies)

Hazard Assessments as Described in M7: What we would like to see

Structure	Chemical Name	Hazard Assessment			Proposed Classification	Action for control
		Literature	Expert Rule-Based Alerts	Statistical-Based Alerts		
Impurity 1 structure	Impurity 1	No data	No Alerts	No Alerts	Class 5	ICH Q3A based on (Q)SAR prediction
Impurity 2 structure	Impurity 2	No data	Aromatic Nitro compound	Nitro group	Class 3	TTC at Release; Option 1; No follow-up Ames test
Impurity 3 structure	Impurity 3	Negative Ames	No *in silico* needed	No *in silico* needed	Class 5	ICH Q3A based on Neg Ames
Impurity 4 structure	Impurity 4	Positive Ames/Animal Carcinogen	No *in silico* needed	No *in silico* needed	Class 1	AI = 157 ug/day per Literature; TTC upstream; Option 2

How is a Classification Provided by Industry Evaluated?

- Hazard assessment Ames studies or Literature justifications are reviewed by PharmTox Assessors
- Hazard assessment (Q)SAR studies are consulted to our Computational Toxicology Consultation Service (CTCS) For impurities classified as Class 1, 2, or 3….

Monitoring Options Outlined in ICH M7 (Sections 8.1, 8.2, and 8.3)

Safety

Ames Test (for Class 3 follow-up on (Q)SAR positive prediction): Must be OECD compliant to support a negative result

Quality

Option 1: Monitor the impurity in the drug substance at TTC
Periodic Verification Testing allowed (8.1): 30% TTC for n=3 consecutive production or n = 6 consecutive pilot scale batches

Option 2: Monitor the impurity in intermediate, starting material or in-process control at TTC

Option 3: Monitor the impurity in intermediate, starting material or in-process control at higher than TTC
Spike/Purge experiments (lab scale) to 30% TTC and where necessary supported by data from pilot or commercial scale batches

Option 4: No monitoring based on design of robust process controls to reduce the risk of impurity level to < 1% TTC

Justification can be based on scientific principles, calculated or measured purge factors, or a combination

Hazard Assessments as Described in M7 and Submitted by Industry for Review

Example Hazard Assessment submitted by Industry for **API-X**:

Structure	Chemical Name	Hazard Assessment			Proposed Classification	Action for control
		Literature	Expert Rule-Based Alerts	Statistical-Based Alerts		
Impurity 1 structure	Impurity 1	No data	No Alerts	No Alerts	Class 5	ICH Q3A based on (Q)SAR prediction
Impurity 2 structure	Impurity 2	No data	Aromatic Nitro compound	Nitro group	Class 3	TTC at Release; Option 1; No follow-up Ames test
Impurity 3 structure	Impurity 3	Negative Ames	No *in silico* needed	No *in silico* needed	Class 5	ICH Q3A based on Neg Ames
Impurity 4 structure	Impurity 4	Positive Ames/Animal Carcinogen	No *in silico* needed	No *in silico* needed	Class 1	AI = 157 ug/day per Literature; TTC upstream; Option 2

Option 1 or 2: Release or Upstream Control How to Calculate TTC

For Individual PMI Impurity:

$$\text{Specification Limit (ppm)} = \frac{\text{Acceptable Intake (µg /day)}}{\text{Maximum Daily Dose (g/day)}}$$

Acceptable Intake (AI) and Maximum Daily Dose (MDD) in this equation are Variables and drug product dependent

Option 1 or 2: Release or Upstream Control How to Calculate TTC, continued

Where to find acceptable intakes and maximum daily dose:

- Is the impurity listed in the M7 Addendum-Class 1
  - Use acceptable intake (AI)
- The clinical duration of use/AI (section 7.3, Table 2)
  - Determined by the labeling; current clinical practice
- Monofunctional alkyl chloride
  - Gets a 10-fold allowable increase in default TTC (see Note 5 in M7)
- MDD of intended drug product
  - Determined by the labeling

Sample Calculation: Impact of Indication, Treatment Duration, and Dose

Impurity 2 (in API X):

- API X is formulated in a product for a non-cancer, chronic treatment (>10 years to lifetime) – ***use 1.5 µg/d Acceptable Intake (AI) per ICH M7 guidance***
- Labeling indicates ***Maximum Daily Dose (MDD) of 150 mg/d***
- Impurity 2 per Option 1 is monitored at a TTC of 10 ppm at release

$$\text{Imp. 2 TTC} = \frac{\text{AI}}{\text{MDD}} = \frac{1.5\ \mu g/d}{0.150\ g/d} = \boxed{10\ ppm}$$

Note: If API X is repurposed for use in a different product, where the ***acceptable intake, indication, or maximum daily dose change***, the TTC could change and the method used could be impacted.

Impurities with Mutagenic Risk

Analytical Methods:

- Require development of sensitive analytical methods with sufficient specificity and sensitivity
- Methods can be HPLC, GC, HPLC-MS, GC-MS etc.
- LOQ should be set at Acceptable Intake (AI) limit or lower (e.g. 30% of AI limit)

Summary

- DMF Holders are expected to perform a hazard assessment for all impurities as outlined in the M7 guideline.
- Classification of an impurity by visual inspection for structural alerts is not compliant with ICH M7
- (Q)SAR assessment and reporting are expected to accompany the hazard assessment impurity classification
- Chemists and PharmTox assessors work collaboratively to ensure that the impurity classification, monitoring, and limit are in accordance with ICH M7.

Questions?

- For questions regarding the content of this presentation, please type them into the “Q&A Box” so that they can be addressed during the panel Q&A after this session.

- To submit questions on this presentation for inclusion in the Follow-on webinar on April 9th , send them by March 19th to: DMFWorkshop2021@fda.hhs.gov

Cross-referenced Talks/Posters

- Please refer to the following posters for cross-referenced materials:

  - ICH M7: Highlight from the Question and Answer Document by David Green

- Please refer to the following presentations on March 3rd and 4th for additional information:
  - *Considerations for Impurity Qualification - ICH Q3A/Q3C/Q3D, RLD, & MDD by Hongbiao Liao*
  - *Application of (Q)SAR and Expert Knowledge for ICH M7 Impurity Classification by Naomi Kruhlak*
  - *Safety Evaluation of Drug Substance Impurities in Generics by Chanchal Gupta*

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