SBIA-DMF Drug Substance Workshop

March 3 & 4, 2021 (Virtual)

Mutagenic Impurities from a Drug Substance Perspective: Highlights from the ICH M7 Question and Answer Draft Document

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PURPOSE

ICH M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk reached step 4 in June of 2014, and the addendum document, with compound specific Acceptable Intakes (AI) reached step 4 in May of 2017. This guidance for the first time outline a variety of approaches to control potentially mutagenetic impurities (PMIs) based on the maximum daily dose, duration of use, and indication of the drug product. The limit to which a PMI is controlled, based on these factors, is defined as the threshold of toxicological concern or TTC.

Since implementation, there has been some confusion with regards to how some of the approaches outlined in the guidance have been interpreted. The ICH M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk: Question and Answer Document, now in step 2, addresses the confusion regarding the interpretation of various section of the original ICH M7 guidance.

Here we highlight four sections covered in the new ICH M7 Question and Answer Document of particular concern to the Agency: Total Mutagenic Impurity Limits; Appropriate Use of the option 4 control strategy; Batch test data less than 30% TTC and spike/ purge studies; and Periodic verification testing as well as defining what is not in the scope of the ICH M7. The highlighted topics here demonstrate that the new ICH M7 Question and Answer Document gives clear guidance for industry on how to fully implement the ICH M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk.

What's *not* in the Scope of ICH M7:

ICH M7 is not intended for the following types of drug substances and drug products:

- Biological/biotechnological, peptides, oligonucleotides, radiopharmaceutical, fermentation, herbal, crude products of animal or plant origin.
- Excipients used in existing marketed products, flavoring agents, colorants, and perfumes.
- Leachables associated with drug product packaging.
- API's 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.

RESULT(S)

1) Total Mutagenic Impurities Limit (Refer to Section 2 of the Guidance and ICH M7 Q&A (Step 2) #7.5)

- The TTC-based acceptable intakes should be applied to each individual impurity. When there are **two Class 2 or Class 3** impurities, individual limits apply. When there are **three or more Class 2 or Class 3** impurities specified on the drug substance specification, total mutagenic impurities should be limited as described in Table 3 (below) for clinical development and marketed products.

Duration of treatment	≤ 1 month	≤ 1 – 12 months	≤ 1 – 10 years	>10 years to lifetime
Total Daily Intake [µg/day]	120	60	30	5

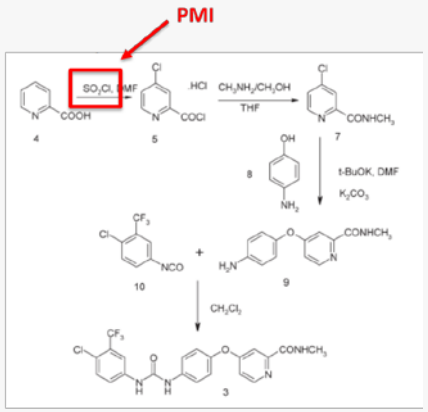
- For combination products each active ingredient should be regulated separately.
- Only specified **Class 2 and 3 impurities** on the drug substance specification are included in the calculation of the total limit. However, impurities with **compound-specific** or **class-related acceptable intake limits (Class 1)** **should not be included** in the total limits of Class 2 and Class 3 impurities. Also, degradation products which form in the drug product would be controlled individually and a total limit would not be applied.

2a) Option 4 Control Strategy (Scenario 1)

Scenario 1: Impurity Introduced Early in the Synthetic Process

(Refer to Section 2 of the Guidance and ICH M7 Q&A (Step 2) #8.1)

When a potential mutagenic impurity (PMI) is introduced early in the synthesis (before the last synthetic step) then the use of Option 4 can be appropriate when a mutagenic impurity is demonstrated to have a negligible risk of being present in the final drug substance (e.g., 1% TTC). The risk assessment can be based on scientific principles alone (e.g., impurity reactivity or solubility), calculated purge factors, (i.e., predicted), measured purge factors (i.e., spike and purge data), or a combination of these approaches, considering the process-relevant conditions. The acceptability of Option 4 will be assessed by authorities on a case-by-case basis.



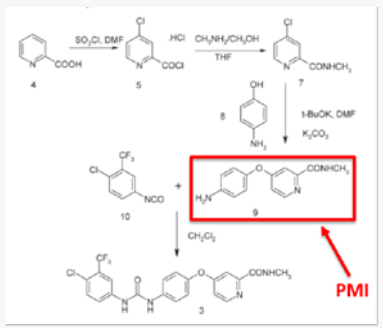
Teasdale et al. *Org. Process Res. Dev.* 2013, *17*, 221–230

2b) Option 4 Control Strategy (Scenario 2)

Scenario 2: Impurity introduced in in the last step of the synthetic step

(Refer to Section 2 of the Guidance and ICH M7 Q&A (Step 2) #8.3)

For potential mutagenic impurities introduced or generated in the last synthetic step, given the proximity to the final product, Option 1 is the preferred control strategy. However, Option 2 and 3 control strategies may be possible, for example, when the crude drug substance is an isolated material which is purified subsequently (e.g., by recrystallization). An Option 4 control strategy for an impurity introduced or generated in the last synthetic step is discouraged and should be reserved for highly reactive species (e.g., thionyl chloride) or materials with low boiling point (e.g., methyl chloride). In case of highly effective purification operations (e.g., chromatography), an Option 4 control approach may also be acceptable for less reactive materials. However, in such cases, the negligible risk of an impurity to be carried to the final product (e.g., 1% TTC) should be justified with experimental data (e.g., spike and purge data under the process-relevant conditions). A justification solely based on calculations (predictions) is not considered sufficient.



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3) Batch Data in PMI Control Strategy

Is test data for a potential mutagenic impurity that is consistently <30% TTC in multiple batches sufficient to justify no testing of that impurity in the control strategy?

(Refer to Section 2 of the Guidance and ICH M7 Q&A (*Step 2*) #8.5)

- **No.** Batch data alone demonstrating that a potential mutagenic impurity is consistently <30% TTC is not sufficient to justify no testing of that impurity. Options 1, 2, or 3 should test either at release or upstream in the process.
- Per ICH M7, If the Option 3 control strategy (upstream control) is chosen, then the following data is recommended to support the proposed upstream limit:
  - Spike/ purge experiment at the proposed limit from laboratory scale experiments and where necessary supported by data from pilot scale or commercial scale batches.
  - Data from multiple batches which is consistently <30% TTC.
- However, if there is negligible risk of the impurity to be present in the drug substance, an Option 4 control strategy may be considered with appropriate justification. See previous slides on the Option 4 control strategy.

4) Periodic Verification Testing

Is periodic verification testing (i.e., skip testing) allowed for Option 2 and 3 control?

(Refer to Section 2 of the Guidance and ICH M7 Q&A (Step 2) #8.4)

- **No.** Periodic verification testing is not appropriate for Option 2 and 3 control. Periodic verification testing is only discussed as a control strategy for Option 1 control in section 8.1 of ICH M7.
- The Option 1 periodic verification testing strategy references ICH Q6A. The Option 1 periodic verification testing concept (per ICH Q6A) should generally be implemented post-approval and applies to testing in the final drug substance.

CONCLUSION(S)

Since implementation, there has been some confusion with regards to how some of the approaches outlined in the guidance have been interpreted. The ICH M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk: Question and Answer Document, now in step 2, addresses the confusion regarding the interpretation of various section of the original ICH M7 guidance.

This poster defined what is not in the scope of the ICH M7 and highlighted four topics covered in the new ICH M7 Question and Answer Document of particular concern to the Agency:

- Total Mutagenic Impurity Limits
- Appropriate Use of the option 4 control strategy (two scenarios: PMI introduced early in the synthesis and during the last synthetic step)
- Batch test data less than 30% TTC and spike/ purge studies
- Periodic verification testing.

The sections that we highlighted demonstrate that the new ICH M7 Question and Answer Document gives clear guidance for industry on how to fully implement the ICH M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk.

SUPPORTING DATA EXPECTATIONS & LINKS:

Spike/ purge studies:
Studies should include batch size of the laboratory scale experiment, proposed limit of PMI, complete analytical method information, (including LOD and LOQ) as well as a results table.

Option 4 purge calculations:

Calculations should be detailed and follow the format outline by Teasdale et al. in *Org. Process Res. Dev.* 2013, *17*, 221–230. Any supporting literature used to justify purge factors should be submitted with the calculations.

Links:

- ICH M7(R1): Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk
- ICH M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk; Question and Answer Draft document.

ACKNOWLEDGEMENTS

Rajan Pragani

Mutagenic Impurities from a Drug Substance Perspective: Highlights from the ICH M7 Question and Answer Draft Document

David Green – Chemist
Barbara Scott ***– Chemist***
CDR David Skanchy ***– Chemist***

On behalf of
Division of Lifecycle API
Office of New Drug Products
Office of Pharmaceutical Quality, FDA/CDER

Purpose

To highlight specific questions from the M7 Q/A document regarding:

- When a total mutagenic total impurity limit is applicable.
- When is it appropriate to use an Option 4 strategy?

  - two scenarios addressed

- Is test data for a potential mutagenic impurity that is consistently <30% TTC in multiple batches sufficient to justify no testing of that impurity in the control strategy?
- Is periodic verification testing (i.e. skip testing) allowed for Option 2 and 3 control?

Brief Background

- **ICH M7:** Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk.
  - Step 4 in June 2014.
- **ICH M7:** Addendum to original guidance with compound specific Acceptable Intakes
  - Step 4 May 2017.
- **ICH M7:** Questions and Answers (Draft) Document
  - Step 2b as of June 2020; public comment phase completed and questions are being addressed by the ICH Expert Working Group.
  - A supporting document for ICH M7 which provides clarification on both safety and chemistry aspects of the guideline.

Not in the Scope of ICH M7

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

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Total Mutagenic Impurities Limit

Acceptable Intakes for Multiple Mutagenic Impurities
(Refer to Section 2 of the Guidance and ICH M7 Q&A *(Step 2)* #7.5)

The TTC-based acceptable intakes should be applied to each individual impurity. When there are two Class 2 or Class 3 impurities, individual limits apply. When there are **three or more** Class 2 or Class 3 impurities specified on the drug substance specification, total mutagenic impurities should be limited as described in Table 3 (below) for clinical development and marketed products.
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Option 4 Control Strategy

- Scenario 1: Impurity Introduced Early in the Synthetic Process

- When a potential mutagenic impurity (PMI) is introduced early in the synthesis (before the last synthetic step) then the use of Option 4 can be appropriate when a mutagenic impurity is demonstrated to have a negligible risk of being present in the final drug substance (e.g., 1% TTC). The risk assessment can be based on scientific principles alone (e.g., impurity reactivity or solubility), calculated purge factors, (i.e., predicted), measured purge factors (i.e., spike and purge data), or a combination of these approaches, considering the process-relevant conditions. The acceptability of Option 4 will be assessed by authorities on a case-by-case basis.

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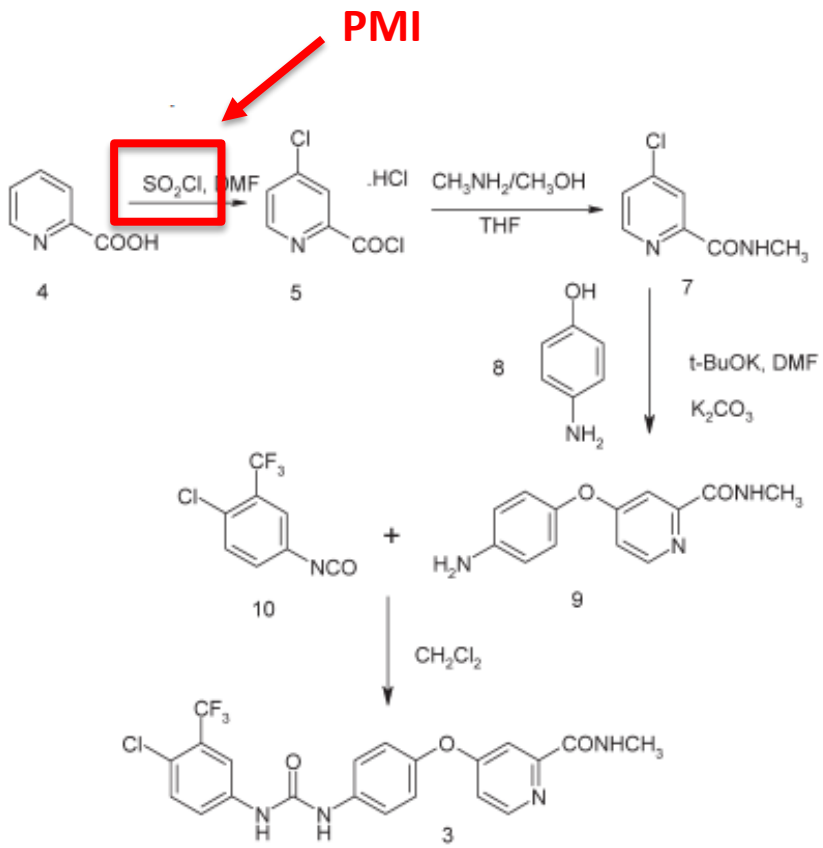

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Option 4 Control Strategy

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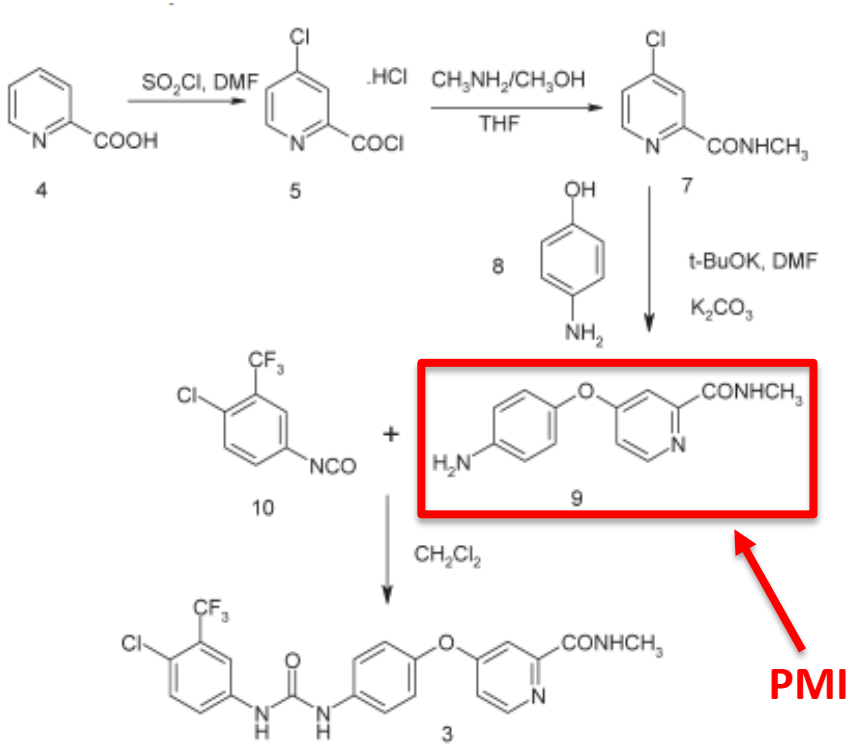

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References:

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- ICH M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk; Question and Answer.

Thank You!

- Send questions regarding this poster to: DMFWorkshop2021@fda.hhs.gov by 2/15/2021 for inclusion in the poster Q&A session on March 4th.
- Follow-on webinar for both posters/presentations on April 9, 2021. Questions can be sent to the above email by 3/19/2021 for the webinar.
- Please refer to the following posters for cross-referenced materials:
  - *Establishing Impurity Acceptance Criteria as Part of Specifications for DMFs Based on Clinical Relevance.* Yongjun Gao, Ramnarayan Randad, David Green, Weixiang Dai, Hongbiao Liao and David Skanchy.
- Please refer to the following presentations on March 3rd and 4th for additional information:
  - *Considerations for Impurity Qualification - ICH Q3A/Q3C/Q3D, RLD, & MDD.* Hongbiao Liao.
  - *ICH M7(R1) – Chemistry and manufacturing control (CMC) Perspective on Impurity Hazard Assessment.* Barbara O. Scott.
  - *Application of (Q)SAR and Expert Knowledge for ICH M7 Impurity Classification.* Naomi L. Kruhlak.