Sharing Drug Substance M7 information to HA and MAH:

Templates

Interpretation of the ICH M7 guideline and other relevant guidelines with regards to ICH M7 data sharing

Version 1
(April 2023)

Contents

New submission (DMF/ASMF & CEP) - Sharing M7 information to HA - Template

Markets: countries that are ICH Members/Observers

Considering the existing guidelines requirements and based on practical experience of APIC Members, it is recommended by APIC to follow the below template for sharing M7 data within the new submission of DMF to HAs, in cases where ICH M7 assessment is required.
The M7 information is typically presented in DMF section 3.2.S.3.2 Impurities. Detailed safety study information can be presented in Module 1 (Additional data or Literature folder) or Module 3 RP DMF (e.g. 3.2.S.2.6, 3.2.S.2.5).

Template is provided on the following pages.

EVALUATION OF (POTENTIALLY) MUTAGENIC IMPURITIES IN LINE WITH THE ICH M7 GUIDELINE

Document ID:

ACTIVE PHARMACEUTICAL INGREDIENT (API)

Name: .....

Material code(s): .....

MANUFACTURER (refers to the manufacturing site)

Name: .....

Address: .....

(Optionally indicate name / function) ***This report was completed by [person / central service]***:

- Name and position: .....
- E-mail address: .....
- Postal address: .....

Declaration:

The current manufacturing process of *(the name of the API)* was assessed for the risk of presence of (potentially) mutagenic impurities in accordance with the requirements of the guideline *ICH M7: Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk.*

All information contained in this report is based on current knowledge and is true and sincere to our actual knowledge.
In case of changes in the manufacturing process, starting materials, suppliers etc. that may affect this evaluation, we will evaluate the impact, revise this document when necessary and inform our customers in case of any changes in the outcome.

The information in this document may be updated as more information becomes available.

Date
(Optionally sign) **Signature and Company stamp**

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1 INTRODUCTION

The synthetic process for manufacturing of *xxx* drug substance was assessed for the risk of presence of (potentially) mutagenic impurities in accordance with the requirements of the guideline *ICH M7: Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk.*

The assessment includes actual and potential impurities originating from the manufacturing process of *xxx* drug substance, including process-related impurities and degradation products. Impurities have been identified and classified in-line with the ICH M7 guideline.
The assessment inlcudes also cohort of concern compounds, i.e., aflatoxin-like- and alkyl azoxy structures. N-Nitrosamines are excluded from this report as the formation and presence of nitrosamines in drug substance *xxx* is the subject of a separate assessment.

Hazard assessment of impurities was performed by conducting database and literature searches for carcinogenicity and bacterial mutagenicity data, or by performing (Q)SAR assessment of impurities for which literature data are not available using

a) Expert-rule based program: *specify the name of the program, version number/year*
b) Statistical-based program: *specify the name of the program, version number/year*

For Class 2 and Class 3 impurities, the concept of threshold of toxicological concern (TTC) was used for calculating the acceptable concentration limit. Considering the maximum daily dose of *xxx* drug substance of *xxx* g/day, *xxx* duration of treatment, and TTC value of *1.5 µg/day*, the following acceptable concentration limit has been calculated for Class 2 and Class 3 impurities in the *xxx* drug substance:

$$\text{Acceptable concentration limit [ppm]} = \frac{\text{TTC}\left[\frac{\mu g}{day}\right]}{\text{daily dose}\left[\frac{g}{day}\right]}$$

Based on the calculation, the acceptable concentration limit of *not more than xxx ppm* for Class 2 and Class 3 impurities in the *xxx* drug substance is considered as safe.
For Class 1 impurities, compound-specific acceptable concentration limit has been calculated considering maximum daily dose of the drug substance.

Please find a Detailed Hazard Assessment Report provided on the following pages. Impurities classification with respect to mutagenic and carcinogenic potential and resulting control actions are performed in line with recommendations of the *ICH M7: Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk* guideline.

2 DETAILED HAZARD ASSESSMENT REPORT

This Hazard Assessment Report describes summary of Hazard assessment of impurities performed in-line with the ICH M7 guideline, including available literature data supplemented with *in silico* predictions for impurities in the *xxx* drug substance synthesis.

3.1 METHODOLOGY

Hazard assessment of impurities in the *xxx* drug substance synthesis involved:

- Initial analysis of actual and potential impurities by conducting database and literature searches for carcinogenicity and bacterial mutagenicity data
- Classification of impurities with respect to mutagenic and carcinogenic potential based on literature data
- (Q)SAR assessment of impurities for which literature data are not available
- Classification of impurities with respect to mutagenic and carcinogenic potential based on (Q)SAR predictions and expert knowledge

3.2 CLASSIFICATION OF IMPURITIES

Classification of substances into classes as proposed by Müller et al. [1] and ICH M7: Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk, guidance.

[1]Müller L., Mauthe R.J., Riley C.M., Andino M.M., De Antonis D., Beels C., DeGeorge J., De Knaep A.G.M., Ellison D., Fagerland J.A., Frank R., Fritschel B., Galloway S., Harpur E., Humfrey C.D.N., Jacks A.S.J., Jagota N., Mackinnon J., Mohan G., Ness D.K., O'Donovan M.R., Smith M.D., Vudathala G., Yotti L., A rationale for determining, testing, and controlling specific impurities in pharmaceuticals that possess potential for genotoxicity, Reg Tox Pharm 44, 198-211, 2006.

Class	Definition	Proposed action for control
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 (appropriate TTC)
3	Alerting structure, unrelated to the structure of drug substance; no mutagenicity data	Control at or below acceptable limits (appropriate TTC) or conduct bacterial mutagenicity assay If non-mutagenic = Class 5 If mutagenic = Class 2
4	Alerting structure, same alert in drug substance or compounds related to the drug substance (e.g., process intermediates) which have been tested and are non-mutagenic	Treat as non-mutagenic impurity
5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity	Treat as non-mutagenic impurity

* 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)

3.3 RESULTS OF ASSESSMENT

Table 1: Summary of Assessment (actual and potential impurities*), including detailed information on control strategies for Class 1, 2 and 3 impurities

Impurity information			Hazard assessment outcome**				Control strategy (for Class 1, 2, 3 impurities)	
Chemical name/ IUPAC name, code name, CAS number (if available)	Structural Formula	Origin (e.g., step of the synthesis, RoS of SM)	Literature/ Database search	*In silico* (expert-rule)	*In silico* (statistical)	ICH M7 Classification (Class 1-5)	ICH M7 Control strategy (Define if Option 1, 2, 3 or 4)	Justification of control strategy***

Actual Impurities:

According to the ICH M7 guideline, "actual impurities include those impurities that are observed in the drug substance above the ICH Q3A reporting threshold".

Potential Impurities:

According to the ICH M7 guideline, potential impurities are components that can be starting materials, reagents and intermediates or impurities that form under storage. Therefore, these impurities are obvious from the reaction scheme or result from theoretical considerations, but are not present in the final DS/DP above the ICH Q3A reporting threshold.

*** Provide rationale for classification and/or references to support proposed classification.*

**** Provide detailed justification of proposed control strategy (see next page).*

RATIONALE FOR CLASSIFICATIONS

Fulfil this part in case of any equivocal or inconclusive results, contradictory studies, etc.

REFERENCES

Add references to the mutagenicity/carcinogenicity studies or other literature to support classification.

JUSTIFICATION OF CONTROL STRATEGY

Control strategy for each Class 1, 2 or 3 impurity should be appropriately justified. Following information is recommended to be provided to support each of the possible control option strategies:

Option 1 control strategy

The following information is recommended to be provided to HA to support the control strategy:

- origin of the impurity and its fate in the process
- calculated acceptable concentration limit
- established specification limit in the API
- analytical method description and validation (reference to section 3.2.S.4.2 and 3.2.S.4.3)
- batch data to support established specification limit
- in case of skip testing: batch data to support (6 consecutive pilot-scale or 3 consecutive commercial-scale batches), levels < 30 % of the acceptable limit

Option 2 control strategy

The following information is recommended to be provided to HA to support the control strategy:

- origin of the impurity and its fate in the process
- calculated acceptable concentration limit
- where it is controlled (raw material, intermediate etc.) and justification
- established specification limit in the raw material/intermediate etc.
- description of analytical method, validation report – reference to RP DMF
- batch data to support established specification limit

Option 3 control strategy

The following information is recommended to be provided to HA to support the control strategy:

- information on calculated acceptable limit
- where it is controlled (raw material, intermediate etc.) and justification
- specification acceptance criteria
- description of analytical method, validation report
- describe fate and purge of impurity
- batch data to support established limit (spiking experiments demonstrating levels < 30 % of acceptable limit in the API)

Option 4 control strategy

The following information is recommended to be provided to HA to support the control strategy:

- origin of the impurity and its fate in the process

- justification that the process is capable to purge the impurity (e.g. purge factor calculation)

New submission (DMF/ASMF & CEP) - Sharing M7 information to MAH - Template

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Hazard assessment of impurities was performed by conducting database and literature searches for carcinogenicity and bacterial mutagenicity data, or by performing (Q)SAR assessment of impurities for which literature data are not available using

a) Expert-rule based program: *specify the name of the program, version number/year*
b) Statistical-based program: *specify the name of the program, version number/year*

For Class 2 and Class 3 impurities, the concept of threshold of toxicological concern (TTC) was used for calculating the acceptable concentration limit. Considering the maximum daily dose of *xxx* drug substance of *xxx* g/day, *xxx* duration of treatment, and TTC value of *1.5 µg/day*, the following acceptable concentration limit has been calculated for Class 2 and Class 3 impurities in the *xxx* drug substance:

$$\text{Acceptable concentration limit [ppm]} = \frac{\text{TTC}\left[\frac{\mu g}{day}\right]}{\text{daily dose}\left[\frac{g}{day}\right]}$$

Based on the calculation, the acceptable concentration limit of *not more than xxx ppm* for Class 2 and Class 3 impurities in the *xxx* drug substance is considered as safe.

For Class 1 impurities, compound-specific acceptable concentration limit has been calculated considering maximum daily dose of the drug substance.

Please find a Summary of the Assessment in form of a table on the following pages, including list of impurities, impurity classification together with summarized rationale of the classification, and control strategy information. Impurities classification with respect to mutagenic and carcinogenic potential and resulting control actions are performed in line with recommendations of the *ICH M7: Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk* guideline. Detailed Hazard Assessment Report is provided in RP DMF section xxx.

2 SUMMARY OF ASSESSMENT

Table 1: Summary of Assessment (actual and potential impurities*)

Impurity information			Hazard assessment outcome				Control strategy (for Class 1, 2, 3 impurities)	
Chemical name/ IUPAC name, code name, CAS number (if available)	Structural Formula	Origin (e.g., step of the synthesis, RoS of SM)	Literature/ Database search	*In silico* (expert-rule)	*In silico* (statistical)	ICH M7 Classification (Class 1-5)	ICH M7 Control strategy (Define if Option 1, 2, 3 or 4)	Brief description of control strategy, including concentration limits applied [ppm], and data to support proposed control strategy**

Actual Impurities:

According to the ICH M7 guideline, "actual impurities include those impurities that are observed in the drug substance above the ICH Q3A reporting threshold".

Potential Impurities:

According to the ICH M7 guideline, potential impurities are components that can be starting materials, reagents and intermediates or impurities that form under storage. Therefore, these impurities are obvious from the reaction scheme or result from theoretical considerations, but are not present in the final DS/DP above the ICH Q3A reporting threshold.

*** Provide brief description of proposed control strategy (see examples on next page).*

*** The following information is recommended to be provided to MAH to support the proposed control strategy:*

Option 1 control strategy

The following information is recommended to be provided to MAH:

- brief information on the origin of the impurity

- information on calculated acceptable limit

- DS specification acceptance criteria

- batch data to support established limit

- in case of skip testing: batch data to support (6 consecutive pilot-scale or 3 consecutive commercial-scale batches, levels < 30 % of the acceptable limit)

Option 2 control strategy

The following information is recommended to be provided to MAH:

- brief information on the origin of the impurity

- information on calculated acceptable limit

- where it is controlled (raw material, intermediate etc.) and justification

- specification acceptance criteria

- optional: batch data to support established limit

Option 3 control strategy

The following information is recommended to be provided to MAH:

- brief information on the origin of the impurity

- information on calculated acceptable limit

- where it is controlled (raw material, intermediate etc.) and justification

- specification acceptance criteria

- optional: fate and purge of impurity, batch data to support established limit (spiking experiments demonstrating levels < 30 % of acceptable limit in the API)

Option 4 control strategy

The following information is recommended to be provided to MAH:

- brief information on the origin of the impurity

- justification of control strategy (justification based on physico-chemical properties and/or purge factor calculation)*

**In case of purge factor calculation, the following data might be shared: starting levels, required purge, calculated purge.*

Examples:

Option 1 *-routine/periodic (choose one) testing on API with a limit of xxx. Analytical testing results are provided in section xxx (LOD = xxx, LOQ=xxx).*

Option 2 *– included on specification of (choose one) raw material/starting material/ intermediate or as an in-process control, with a limit of xxx.*

Option 3 *– included on specification of (choose one) raw material/starting material/ intermediate or as an in-process control, with a limit of xxx.*

Option 4 *– justification based on physico-chemical properties and/or purge factor calculation applied, including information on permitted level in API.*