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M7 Implementation Working Group

ICH M7(R2) Guideline:
ASSESSMENT AND CONTROL OF DNA REACTIVE (MUTAGENIC) IMPURITIES IN PHARMACEUTICALS TO LIMIT POTENTIAL CARCINOGENIC RISK

Questions and Answers

M7(R2) Q&As

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In order to facilitate the implementation of the ICH M7(R2) Guideline, the ICH M7 Implementation Working Group has developed a series of Q&As:

ICH M7(R2) Q&As
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M7(R2) Q&As	Approval by the Assembly under *Step 4*	**24 May 2022**

References

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Barber, et. al. A consortium-driven framework to guide the implementation of ICH M7 Option 4 control strategies. Reg. Tox. and Pharm. *90*, 2017. 22-28.
ICH Q3A(R2) Impurities in New Drug Substances 25 October 2006
ICH Q3B(R2) Impurities in New Drug Products 2 June 2006
ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances 6 October 1999
ICH S2(R1) Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use 9 November 2011
ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals 18 November 2009
ICH M4Q(R1) CTD on Quality 12 September 2002
ICH M4S(R2) CTD on Safety 20 December 2002

ICH M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk 1 June 2017
OECD Validation (http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2007)2&doclanguage=en) 2007
OECD (Q)SAR Model Reporting Format (QMRF) (https://publications.jrc.ec.europa.eu/repository/bitstream/JRC107491/kjna28713enn.pdf) 2017

TABLE OF CONTENTS

PREFACE

Since the ICH M7 Guideline was finalized, worldwide experience with implementation of the recommendations for DNA reactive (mutagenic) impurities has given rise to requests for clarification relating to the assessment and control of DNA reactive (mutagenic) impurities.

This Question and Answer (Q&A) document is intended to provide additional clarification and to promote convergence and improve harmonization of the considerations for assessment and control of DNA reactive (mutagenic) impurities and of the information that should be provided during drug development, marketing authorization applications and/or Master Files submissions.

The scope of this Q&A document follows that of ICH M7.

“Applicant” is used throughout the Q&A document and should be interpreted broadly to refer to the marketing authorization holder, the filing applicant, the drug product manufacturer, and/or the drug substance manufacturer.

1. INTRODUCTION

#	Questions	Answers
1.1	Note 1 provides general guidance on the relationship of ICH M7 with ICH Q3A and Q3B. The use of both “mutagenic potential” and “genotoxic potential” in Note 1 is confusing. Are these terms considered interchangeable?	No. The terms “mutagenic potential” and “genotoxic potential” are not interchangeable. Mutagenic potential refers to the ability of a compound to induce point mutations (i.e., bacterial reverse mutation assay), while genotoxic potential refers to mutagenic, clastogenic or aneugenic potential. ICH M7 focuses specifically on mutagenicity.
1.2	What are the expectations for evaluation of the mutagenic potential for an impurity where the amount of impurity is less than or equal to 1 mg daily dose?	In the context of ICH M7, (Quantitative) Structure-Activity Relationships ((Q)SAR) is considered an appropriate initial evaluation of mutagenic potential of an impurity at a daily dose of ≤ 1 mg. When a structural alert is identified, a follow-up *in vitro* evaluation (e.g., bacterial reverse mutation assay) could be conducted, or the impurity could be controlled by Threshold of Toxicological Concern (TTC). Negative results in either evaluation would classify the impurity under Class 5. The result of the bacterial reverse mutation assay overrules the (Q)SAR prediction. Additionally, impurities should not be assigned to Class 5 based solely on the absence of structural alerts by visual evaluation alone. There is an expectation that structural alert assessment will be conducted using (Q)SAR prediction.

1.3	What are the expectations for evaluation of the genotoxic potential for an impurity where the amount of impurity exceeds 1 mg daily dose?	In the context of Note 1 of the ICH M7 guideline, 1 mg refers to an absolute amount of an impurity, irrespective of the identification or qualification thresholds outlined in the ICH Q3A/B guidelines. In cases where the amount of impurity is >1 mg daily dose for chronic administration, and an impurity generated negative predictions in two appropriate (Q)SAR systems, a minimum screen of genotoxicity studies (point mutation and chromosomal aberration) could be considered.
1.4	If an impurity generates negative predictions in two appropriate (Q)SAR systems and is present at a level less than or equal to 1 mg daily dose, is further genetic toxicity testing warranted?	No. If an impurity generates negative predictions in two appropriate (Q)SAR systems and is present at a level ≤1 mg/day, further genetic toxicity testing is not warranted.

2. SCOPE OF GUIDELINE

#	Questions	Answers
2.1	Are semi-synthetic drug substances and drug products included in the scope of ICH M7?	Yes, for certain cases. If a semi-synthetic drug substance, as defined in ICH Q11, is manufactured using steps that could introduce mutagenic impurities or degradation products (e.g., post-modification of a fermentation product or late-stage introduction of a linker) a risk assessment is warranted. The following compounds used in the manufacturing process of semi-synthetic drug substances and drug products should be considered within the scope of the application of ICH M7: • chemically-synthesized intermediates and actual impurities therein • reagents

3. GENERAL PRINCIPLES

#	Questions	Answers
3.1	Should non-mutagenic, carcinogenic impurities be controlled according to ICH M7?	No. Carcinogens that are negative in the bacterial reverse mutation assay do not have a DNA reactive mechanism of carcinogenicity and therefore are not in scope of the ICH M7 guideline (e.g., acetamide and hydroxylamine).
3.2	Should mutagenic, non-carcinogenic impurities be controlled according to ICH M7?	No. Mutagens that are demonstrated to be non-carcinogenic in appropriate and well-conducted animal bioassays will be classified as Class 5 impurities.

4. CONSIDERATIONS FOR MARKETED PRODUCTS

#	Questions	Answers
4.1	What does "significant increase in clinical dose" mean in "4.3 Changes to the Clinical Use of the Marketed Products"?	Any increase in dose of the active pharmaceutical ingredient (API) that would increase any mutagenic impurity to levels above the acceptable limits is considered significant (see Tables 2 and 3 and the addendum of ICH M7). In such cases a re-evaluation of the mutagenic impurity limits is recommended.

5. DRUG SUBSTANCE AND DRUG PRODUCT IMPURITY ASSESSMENT

#	Questions	Answers
5.1	No Q&A drafted on this section	

6. HAZARD ASSESSMENT ELEMENTS

#	Questions	Answers
6.1	What information and/or documentation should be provided to regulatory agencies to sufficiently demonstrate validation of (Q)SAR models that are developed in-house or are not commonly used?	Section 6 of ICH M7 states that "(Q)SAR models utilizing these prediction methodologies should follow the general validation principles set forth by the Organization for Economic Co-operation and Development (OECD)" [OECD Validation, 2007]. In the context of ICH M7, the OECD Principles of (Q)SAR Validation are: 1. A defined endpoint – The model should be trained using experimental data generated according to the standard OECD protocol for the *in vitro* Bacterial Reverse Mutation Assay. 2. An unambiguous algorithm – The algorithm used to construct the model should be disclosed. It should be clear whether the model is considered statistical (constructed via machine learning) or expert rule-based (created from human expert-derived knowledge). 3. A defined domain of applicability – It should be described whether a test chemical falls within the model's applicability domain and how the applicability domain is calculated. The user should be warned when the model does not have enough information to make a reliable prediction on a chemical. 4. Appropriate measures of goodness-of–fit, robustness and predictivity – The model should be evaluated and shown to be sufficiently predictive of bacterial reverse mutagenicity. Standard validation techniques that should be used are recall, cross-validation, and external validation. Evidence that the model has not been over-fit should also be provided. 5. A mechanistic interpretation - Is there adequate information to allow an assessment of mechanistic relevance to be made (e.g., specific descriptors)? For any system as minimum requirement to demonstrate how each model follows these principles and to understand how a (Q)SAR model was developed and validated, the sponsor is expected to provide the OECD (Q)SAR Model Reporting Format (QMRF) [OECD QMRF, 2017] on request by the regulatory agency. This template summarizes and reports key information on (Q)SAR models, including the

		results of any validation studies as well as provides supplementary information on applicability of the model to a given chemical. Agencies may request this information depending on the experience of the specific agency with the specific models.
6.2	When an out of domain or non-coverage result is obtained from one of the two (Q)SAR models as described in ICH M7, can the impurity be classified as a Class 5 impurity?	No, an out of domain or non-coverage result from one of the two (Q)SAR models requires additional assessment to classify the compound as a class 5 impurity. Given that the relationship between chemical structure and DNA reactivity is well understood, it is unlikely that a structure with mutagenic potential would be associated with an out of domain result. However, expert review can provide reassurance in assignment of such impurities to class 5. Expert review may include one or a combination of the following [Amberg et. al., 2019]: 1. Comparison to structurally similar analogs for which bacterial reverse mutation assay data are available (read-across approach). 2. Expert review of the chemical structure to determine if there is potential for the chemical to react with DNA. 3. (Q)SAR output from an additional validated model (see Question 6.1) of the same methodology (i.e., expert rule-based or statistical) that generates a prediction that is within its applicability domain.
6.3	In a case where an impurity is demonstrated to be negative in an Ames test but positive in a clastogenicity study (e.g., chromosomal aberration test), how would the impurity be classified per the ICH M7 classification system?	If an impurity tests negative in an Ames assay, it is considered a Class 5 impurity. Addressing positive results in a clastogenicity assay is out of scope of ICH M7.
6.4	Please clarify the rationale for the tests included under Note 3 as a follow-up to	If an impurity is positive in the Ames test, and levels of the impurity cannot be controlled to an appropriate acceptable limit, an *in vivo* follow-up test with mutagenic

	investigate the *in vivo* relevance of *in vitro* mutagens.	endpoint (mutagenicity) should be used. The other follow-up tests outlined in Note 3 are also acceptable when scientific rationale (as indicated in Note 3) is provided to support their use. For any of the above tests, adequate exposure should be demonstrated in line with ICH S2.

7. RISK CHARACTERIZATION

#	Questions	Answers
7.1	If an Ames positive impurity is subsequently tested in an appropriate *in vivo* assay and the results are negative, is that sufficient to demonstrate lack of *in vivo* relevance?	Yes. A well conducted and scientifically justified *in vivo* study (see question 6.4 in this document) is sufficient to demonstrate lack of *in vivo* relevance. If the results of the *in vivo* study are negative, the impurity can be assigned to ICH M7 Class 5.
7.2	If an Ames positive impurity cannot be controlled to an acceptable limit and is subsequently tested in an appropriate *in vivo* assay and the results are positive, does that support setting compound-specific impurity limits?	When a mutagenic impurity cannot be controlled to the TTC (or less than lifetime-based limit), results from an appropriate *in vivo* assay could complement the available data for a weight of evidence approach to support a higher limit on a case by case basis. However, *in vivo* gene mutation assays alone are currently not validated to directly assess cancer risk because the endpoint is mutation and not carcinogenicity (i.e., they are used for hazard identification).

7.3	Can a less than lifetime (LTL) approach be applied to acceptable intakes (AIs) or permissible daily exposures (PDEs) using the same ratio as in Table 2?	The LTL approach can be applied to compounds with exposure limits based on the TTC or a compound/class specific AI. However, this approach is not applicable to PDEs as linearity of dose duration response is not considered sufficiently demonstrated for threshold related mechanisms. Higher levels of exposure for short-term exposure (30 days or less) may be acceptable on a case by case basis.
7.4	Why was HIV disease moved to the “Treatment duration of >10 years to lifetime” in the clinical use scenarios table? How should this change be implemented?	The treatment duration category was changed because of advances in the clinical treatment of HIV disease. To avoid disruption of supply of HIV drugs already on the market, this change will not be applied to currently marketed products. For example, when a new drug substance supplier is proposed, the acceptable intake would remain at 10 µg/day in cases where the drug substance produced by this supplier, using the same route of synthesis, is a component of an existing drug product marketed in the specific region (see ICH M7 Section 4.1). For HIV treatment-related regulatory submissions 18 months after the date that the M7 Q&A reached Step 4, the 1.5 µg/day or other appropriate acceptable intake will be applied in the following situations: • new drug substances and new drug products during their clinical development and subsequent applications for marketing • changes to the drug substance synthesis resulting in new impurities or increased acceptance criteria for existing impurities • changes in the formulation, composition or manufacturing process resulting in new degradation products or increased acceptance criteria for existing degradation products • introduction of a new source of the drug substance through a drug master file (DMF) from a DMF holder who has not had a previously accepted DMF in the relevant region • changes made to a specific synthetic step as described in ICH M7 Section 4.1 • a newly discovered Class 1 or Class 2 impurity, a structure in the cohort of concern, or new relevant impurity hazard data, as described in ICH M7 Section 4.4

7.5	Does “Table 2: Acceptable Intakes for an Individual Impurity” apply when three or more Class 2 or Class 3 impurities are specified in the drug substance specification?	Yes. In this scenario, a limit for each “Individual Impurity” should be listed in the drug substance specification as per limits provided in Table 2 (for example >10 years to lifetime not more than (NMT) 1.5 µg/day). Additionally, a limit for “Total Mutagenic Impurities” should be listed in the drug substance specification as per limits provided in Table 3 (for example >10 years to lifetime NMT 5 µg/day). As stated in the guidance, compound-specific or class-related acceptable limits (Class 1) and degradation products which form in the drug product are excluded from total mutagenic impurity limits.

8. CONTROL

#	Questions	Answers
8.1	When is it appropriate to use an Option 4 control strategy?	Use of Option 4 is appropriate when a mutagenic impurity has a negligible risk of being present in the final drug substance. The risk can be considered negligible if predictive purge calculations based on scientific principles (e.g., impurity reactivity or solubility) result in impurity levels < 1% of TTC or AI. When predictive purge calculations result in impurity levels ≥ 1% of TTC or AI, measured purge factors (i.e., spike and purge data) showing impurity levels less than 10% of TTC or AI should be provided to justify Option 4 control. The process-relevant conditions should be considered for the purge calculation and the generation of analytical data. The acceptability of Option 4 will be assessed by authorities on a case-by-case basis, including additional requests for supporting information. See also question 8.3 in this document for impurities introduced in the last step.

8.2	When predictive purge calculations are used for Option 4 control, what elements should be considered?	When using predictive purge calculations for Option 4 control, the following elements should be considered: • Predictive purge calculations should be based on the drug substance manufacturing process as described in the application and should consider reactivity, solubility, volatility, and other factors of the impurity in each step. The predictive purge calculation should use conservative values and methodology, since predictive purge often does not rely on experimental confirmation. Example predictive purge calculation approach based on scientific principles has been described [Teasdale et. al , 2013; Barber et. al., 2017]. Predictive purge calculations can be paper-based or software-based. • The amount of information (i.e., impurity reactivity or solubility data, spike and purge data under the process relevant conditions) to justify a predictive purge calculation approach should be guided by knowledge of the manufacturing process, risk to the final drug substance, and the stage of drug development. • A predictive purge calculation justification submitted in an application could range from a high-level summary to detailed information on the calculation (e.g., scientific justification for individual purge factors) and other supporting data. More detailed information on the calculation is expected when the predicted level of the impurity in the drug substance approaches the TTC or AI. Even if not submitted, information on how each individual purge factor is derived should be available upon request.

8.3	What is meant by "for impurities introduced in the last synthetic step, an Option 1 control approach would be expected unless otherwise justified" in section 8.2 Considerations for Control Approaches?	For mutagenic impurities introduced or generated in the last synthetic step, given the proximity to the final product, Option 1 control approach is preferred. However, Option 2 and 3 control approaches may be possible when appropriately justified. The control strategy may be influenced by the presence of a subsequent recrystallization step, a highly effective purification operation (e.g., chromatography or well-defined crystallization), the reactivity (e.g., highly reactive reagents such as thionyl chloride) and physical characteristics of the impurity (e.g., low boiling point such as methyl chloride) and the availability of data (analytical data supporting the purge assessment). In most cases, for mutagenic impurities introduced or generated in the last synthetic step, the justification of an Option 4 control approach solely based on prediction is not sufficient and supporting analytical data should be provided (see Q&A 8.1).
8.4	Is periodic verification testing (i.e., skip testing) allowed for Option 2 and 3 control approaches?	No. Periodic verification testing is not appropriate for Option 2 and 3 control approaches. In section 8.1 of ICH M7, periodic verification testing is only discussed as a control strategy when using Option 1 control approach. 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.
8.5	If batch analysis data on the drug substance for a mutagenic impurity is consistently <30% TTC or AI in multiple batches, is that sufficient to justify no specification of that impurity in the control strategy?	No. Batch data alone demonstrating that a mutagenic impurity is consistently <30% TTC or AI is not sufficient to apply an Option 4 control strategy. 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 question 8.1 and 8.2 for recommendations on supporting an Option 4 control strategy.

8.6	What scale considerations are relevant when generating analytical data in support of control Options 3 and 4?	Lab scale experiments are typically sufficient when generating measured purge factors or when defining in-process control points. These studies should employ conditions representative of the final process as described in the application and should consider the potential impact of scale and equipment related differences between the laboratory and production environment (e.g., the effects of mixing on impurity levels in heterogeneous systems, the quality of liquid-liquid phase separations, etc.). In the case of observed scale dependencies, confirmatory testing on batches manufactured at pilot or commercial scale may be advisable. There is no expectation to perform spiking studies at pilot or commercial scale.

9. DOCUMENTATION

#	Questions	Answers
9.1	If (Q)SAR predictions are made during drug development, should they be repeated for the marketing application?	(Q)SAR models developed for use under ICH M7 are generally updated regularly with new bacterial reverse mutagenicity assay data and more refined structural alerts. A Sponsor is not expected to update their (Q)SAR assessment during drug development unless there is a safety concern such as when newly available bacterial reverse mutagenicity assay data and/or mechanistic knowledge suggest that the prediction is incorrect. As an example, in cases where there is reason to question the outcome of a negative prediction (e.g., an aromatic amine is present, but the model gave a negative prediction), a reassessment is recommended. It is recommended that the sponsor re-run (Q)SAR predictions prior to the initial marketing application to ensure predictions reflect the most current data available. If the marketing application is later submitted in other regulatory jurisdictions, reassessment may be considered. Reassessment may also be considered if the predictions made for the initial global marketing application did not use a recent version of the software. In general, predictions generated with models developed prior to ICH M7's publication in 2014 are considered unacceptable.

9.2	For marketing applications, what content and Common Technical Document (CTD) placement recommendations could improve the clarity of an ICH M7 risk assessment and control strategy?	In Module 2, a brief summary of the ICH M7 risk assessment and control strategy should be included (sections 2.3 and 2.6). In Module 3, the ICH M7 risk assessment and control strategy should be provided in detail. This type of information is recommended to be placed in the CTD locations per the ICH M4Q Guidance and related Q&A (e.g., 3.2.S.3.2 Impurities or 3.2.S.4.5 Justification of Specification for drug substance, and 3.2.P.5.5 Characterization of Impurities or 3.2.P.5.6 Justification of Specification for drug product). A table summary of the ICH M7 hazard assessment and ICH M7 impurity control strategy is recommended to improve clarity. • Information recommended for an ICH M7 hazard assessment table includes impurity chemical structure, individual (Q)SAR results (pos/neg predictions, out-of-domain), bacterial reverse mutagenicity assay results (pos/neg, if available), ICH M7 impurity class (1-5) assignment, and supporting information (e.g., information/links for bacterial reverse mutagenicity assays, literature reports, (Q)SAR expert analysis, etc.). The *in silico* systems used (name, version, endpoint) can also be noted. • Information recommended for an ICH M7 impurity control strategy table includes impurity origin (e.g., synthetic step introduced, degradant, etc.), ICH M7 class, purge factors (e.g., measured or predicted), ICH M7 control Option (1-4), control strategy (i.e., including in-process or compound testing rationale), and supporting information (e.g., information/links for justifications, calculations). The maximum daily dose, TTC, and proposed duration of treatment can also be noted. • Additionally, it is recommended that compound code names be cross-referenced, if Module 3 and Module 4 (including toxicity study reports) use different compound naming conventions. In Module 4, full safety study-related information on impurities (e.g., bacterial reverse mutagenicity assay reports, (Q)SAR reports, other genotoxicity test reports, additional testing, etc.) should be included to support the risk assessment and control strategy. This information is often placed in section 4.2.3.7.6 Impurities (see ICH M4S for additional information) and can be cross-referenced to Module 3 by hyperlinks.

10. ILLUSTRATIVE EXAMPLES

#	Questions	Answers
n/a	No Q&A drafted on this section	

11. GLOSSARY

#	Questions	Answers
n/a	No Q&A drafted on this section	