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ICH guideline M7 on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk - questions & answers

Step 2b

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M7 Implementation Working Group

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

Questions and Answers

Version: 29 June 2020

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

Code	History	Date
M7 Q&As	Endorsement by the ICH Assembly under *Step 2a.* Endorsement by the ICH Regulatory members of the Assembly under *Step 2b*. Release for public consultation.	**29 June 2020**

References

Amberg, et. al. Principles and procedures for handling out-of-domain and indeterminate results as part of ICH M7 recommended (Q)SAR analyses. Reg. Tox. and Pharm. *102*, 2019. 53-64.

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

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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.

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 both mutagenic and clastogenic 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	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 recommended?	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.

1.4	What are the expectations for evaluation of the genotoxic potential for an impurity where the amount of impurity exceeds 1 mg daily dose?	In cases where the amount of impurity is >1 mg daily dose for chronic administration, regardless of the impurity classification, a minimum screen of genotoxicity studies (point mutation and chromosomal aberration) can be considered.

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 is manufactured using steps that could introduce mutagenic impurities or degradants (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 guidance (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 treated similarly to 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). 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 – Describe whether a test chemical falls within the model's applicability domain and how it is calculated. It should warn the user 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 developed in house or not commonly used, to demonstrate how each model follows these principles and to understand how a (Q)SAR model was developed and validated, submission of the OECD (Q)SAR Model Reporting Format (QMRF) [OECD QRMF, 2017] for each model used should accompany each regulatory submission. A harmonized template for the QMRF was developed by the

		Joint Research Centre (JRC) and EU Member State authorities. 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.
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. Out of domain or non-coverage is not considered equivalent to class 5. Additional assessment is warranted. 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 study 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 investigate the *in vivo* relevance of Ames mutagen.	If an impurity is positive in the Ames test, an *in vivo* follow-up test with mutagenic endpoint (mutagenicity) should be used. The other follow-up tests outlined in Note 3 are also acceptable when scientific rationale 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 clearly 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* mutagenic relevance. If the results of the *in vivo* study are clearly negative the impurity can be assigned to ICH M7, Class 5.
7.2	If an Ames positive impurity is subsequently tested in an appropriate *in vivo* assay and the results are positive, does that support setting compound-specific impurity limits?	No. *In vivo* gene mutation assays 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). Results from these tests could identify mode of action and/or direct further testing strategy to complement the available data for a weight of evidence approach.
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. 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 would 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 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 would 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 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 supplier 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 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, 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 purge factors. An example predictive purge calculation approach based on scientific principles has been described [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. 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 approach would be expected unless otherwise justified" in section 8.2 Considerations for Control Approaches?	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.
8.4	Is periodic verification testing (i.e., skip testing) allowed for Option 2 and 3 control?	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.

8.5	If test data (i.e., in-process, intermediate, or drug substance impurity test data) for a potential mutagenic impurity is consistently <30% TTC in multiple batches, is that sufficient to justify no testing of that impurity in the control strategy?	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, and 3 should test either at release or upstream in the process. 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 experimental 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 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.

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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 (see below). 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. 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). 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 often placed in section 3.2.S.3.2 Impurities; however, it is sometimes placed in other CTD locations per ICH M4Q guidance. 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, (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, 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.

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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	

M7 Q&A Support Document

Note: The following is an extract of the M7(R2) draft Guideline and is made available as a Support Document to the M7 Q&A question #7.4. The full M7(R2) draft Guideline will be made available for public consultation separately. Please refer to the ICH website for further information regarding the status of the M7(R2) draft Guideline.

Note 7 **Table 4**: Examples of clinical use scenarios with different treatment durations for applying acceptable intakes

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	1.5

Disease (COPD), cystic fibrosis, seasonal and perennial allergic rhinitis, HIV[3]	

[1] This table shows general examples; each example should be examined on a case-by-case basis. For example, 10 µg/day may be acceptable in cases where the life expectancy of the patient may be limited e.g., severe Alzheimer's disease, even though the drug use could exceed 10 year duration.

[2] Intermittent use over a period >10 years but based on calculated cumulative dose it falls under the >1-10 year category.

[3] ~~HIV is considered a chronic indication but resistance develops to the drugs after 5-10 years and the therapy is changed to other HIV drugs.~~ Changed in M7(R2) from 1-10 years to lifetime because of clinical treatment advances. See Q&A.