**ICH M7 Step 1 Document**
**(15 November 2011, EWG Sevilla Meeting)**

# Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

## 1. INTRODUCTION

The synthesis of drug substances involves the use of reactive chemicals, solvents, catalysts, and other processing aids. As a result of chemical synthesis or subsequent degradation, low levels of impurities reside in all drug substances and associated drug products. While ICH Q3A(R2): Impurities in New Drug Substances and Q3B (R2): Impurities in New Drug Products provide guidance for the qualification and control for the majority of the impurities, limited guidance is provided for those impurities that are DNA reactive. The purpose of this guidance is to provide a practical framework that can be applied for the identification, categorization, qualification, and control of these mutagenic impurities to limit potential carcinogenic risk. This guidance is intended to complement ICH Q3A(R2), Q3B(R2) (Note needed?), and ICH M3(R2): Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorizations for Pharmaceuticals.

This guidance emphasizes considerations of both safety and quality risk management in establishing levels of mutagenic impurities that pose minimal carcinogenic risk. It outlines recommendations for assessment and control of mutagenic impurities that reside or are reasonably expected to reside in final drug substance or product, taking into consideration the intended conditions of human use.

## 2. SCOPE OF GUIDELINE

This document is intended to provide guidance for developers of investigational new drug applications for new drug substances during development, and their associated drug products during and after marketing. It also applies to new amendments for existing applications where changes to the drug substance synthesis result in new impurities or higher specified levels of existing impurities for which only the impacted impurities would require evaluation. This guidance would also apply to new applications associated with formulation changes if the formulation change results in new degradants or higher specified levels of existing degradants for which only the impacted degradants would require evaluation. This guidance would also apply to new applications for previously approved products for changes in indication, patient population, or dosing regimen if the change significantly affects the acceptable cancer risk.

This guidance does not apply to drug substances or drug products for the following classes (ICH Q3A/B):

- biological/biotechnological
- peptide
- oligonucleotide

- radiopharmaceutical
- fermentation products
- herbal products
- crude products of animal or plant origin

A notable exception would be when these products are chemically modified (e.g., addition of organic chemical linkers, semi-synthetic products) for which associated organic impurities could be assessed.

This guidance does not apply to those products intended for advanced cancer indications as outlined in ICH S9. Additionally, this guidance does not apply to products where the drug substance itself is genotoxic. In these cases, mutagenic impurities should be managed as ordinary impurities per ICH Q3A/B.

This guidance does not apply to impurities in excipients that are already used in marketed drug products nor for manufacturing changes associated with these excipients. This guidance applies to new excipients used for the first time in a drug product (Note needed?).

Application of this guidance to leachables associated with drug product packaging is not intended, but the risk assessment principles of this guidance for limiting carcinogenic risk can be used if warranted.

## 3. GENERAL PRINCIPLES

In the current context, the classification of a compound (impurity) as genotoxic in general means that there are positive findings in established *in vitro* and/or *in vivo* genotoxicity tests. The focus of this guidance is on DNA reactive substances that have a potential to directly cause DNA damage when present at low levels leading to mutations and therefore, potentially causing cancer. This type of mutagenic carcinogen is usually detected in a bacterial reverse mutation test (Ames test). Other types of genotoxicants that are Ames negative typically have thresholded mechanisms and usually do not pose carcinogenic risk in humans at the level ordinarily present as impurities (Kirkland *et al.,* Additional references). Therefore to limit human cancer risk associated with potentially mutagenic impurities, the Ames test is used to assess the mutagenic potential/effect and the need for controls. Structure-based assessments are useful for predicting Ames outcomes based upon the established knowledge base. There are a variety of approaches to conduct this evaluation including a review of the available literature, expert knowledge, and/or computational toxicology assessment.

A threshold of toxicological concern (TTC) was developed to define a common dose for any unstudied chemical that will not pose a risk of carcinogenicity or other toxic effects (Munro *et al.,* 1999; Kroes and Kozianowski, 2002). For application of a TTC in the assessment of acceptable limits of mutagenic impurities in drug substances, a value of 1.5 μg/day corresponding to a $10^{-5}$ excess lifetime risk of cancer, can be justified. The methods by which the TTC is based upon are generally considered very conservative since they involved a simple linear extrapolation from the dose giving a 50% tumor incidence ($TD_{50}$) to a 1 in $10^6$ incidence,

using $TD_{50}$ data for the most sensitive species and most sensitive site of tumor induction (several "worst case" assumptions) (Munro *et al.,* 1999). Some structural groups were identified to be of such high potency that intakes even below the TTC would be associated with a potential for a significant carcinogenic risk (Cheeseman *et al.,* 1999; Kroes *et al.,* 2004). This group of high potency mutagenic carcinogens ("cohort of concern") comprises aflatoxin-like-, N nitroso-, and azoxy compounds.

During clinical development, it is expected that control strategies and approaches will be less developed in earlier phases where patient populations are smaller and overall development experience is limited. This guidance bases acceptable limits of mutagenic impurities on established risk assessment strategies. Acceptable risk during the early development phase is set at approximately one additional cancer per million. For later stages in development and marketed products when efficacy has been shown, acceptable increased cancer risk is set at approximately one in one hundred thousand. These risk levels represent a small theoretical increase in risk when compared to human overall lifetime incidence of developing any type of cancer, which is in the range of 1 in 4 (Reference needed). It is noted that established cancer risk assessments are based on lifetime exposures. Less than lifetime exposures both during development and marketing can have higher acceptable limits of impurities and still maintain comparable risk levels.

Where a risk has been identified for an impurity, an appropriate control strategy leveraging process understanding and/or analytical controls should be developed to ensure mutagenic impurities are at or below the acceptable cancer risk level.

There may be cases when a mutagenic impurity is also a metabolite of the drug substance. In such cases, the impurity is considered qualified provided that total exposure as a metabolite is at higher exposures than would be achieved just from the impurity (ICH Q3A/Q3B).

## 4. CONSIDERATIONS FOR CONDUCTING AN ASSESSMENT

### 4.1 Applications for a new drug substance and associated drug product

This document is intended to provide guidance for registration applications for new drug substances and their associated drug products. In addition, application of this guidance for products in clinical development is also intended.

### 4.2 Post approval changes for marketed products approved before and after issuance of M7

It is important to assess risk of mutagenic impurities when changes are made to marketed products. These changes may include for example, modification to the synthetic processes, formulation changes, clinical indications and patient populations.

- **CMC changes**
  - Change to drug substance manufacturing process (e.g., change outside of the regulatory process description)

- Changes to manufacturing process should be assessed to determine whether there are any new mutagenic impurities or increase in existing mutagenic impurities. Regulatory submissions associated with such changes should include a summary of the assessment and if appropriate an updated control strategy.

- Changes to drug product (e.g., change in excipients or composition, manufacturing process, dosage forms, combination products (e.g. tablet to IV to capsule).
  - Changes to the drug product should be assessed to determine whether there are any new mutagenic degradants or increase in existing mutagenic degradants. Regulatory submissions associated with such changes should include a summary of the assessment and if appropriate an updated control strategy.
  - Drug substance associated with such drug products, do not require reassessment if there are no changes to the drug substance manufacturing process.

- **Clinical changes**

  - Changes in clinical dosing regimen to an approved product can involve dose, dosing frequency, duration and administration route. A re-evaluation should be considered if there is a significant increase in dose or treatment duration that suggests the potential for increased carcinogenic risk associated with the presence of a low level impurity. Conversely, re-evaluation is not necessary where the new treatment duration is intended for shorter term use. A re-evaluation based on a new intended route of administration is not necessary based on the very conservative nature of the lifetime excess cancer risk levels that should be applicable to low level mutagenic impurities administered by any route.

  - The clinical application of an approved product for a new indication or patient population could lead to a re-evaluation depending on the nature of the change. Assuming no changes to human exposure, a re-evaluation is not necessary for changes to new indications for severe life-threatening or debilitating diseases and where the potential benefits are expected to outweigh potential carcinogenic risks of low level impurities. A re-evaluation should be considered when there is a significant change in the approved product indication e.g. treating a severe disease to a less serious longer term condition. This consideration can be additionally influenced by the need to evaluate an accompanying change in dosing regimen (e.g., use of potentially higher doses, longer treatment durations) for the new indication. Given the very conservative nature of the lifetime excess cancer risk levels, a re-evaluation is not necessary if the product expands to new target patient populations (e.g. pediatrics).

### 4.3 Special considerations for CMC changes to products approved prior to M7

When a portion of the manufacturing process is changed, the assessment of risk from mutagenic impurities should be limited to impurities formed during that portion of the process. It is sufficient to assess whether mutagenic impurities formed during that step are increased and whether any new mutagenic impurities result from the change.

When a new drug substance supplier is proposed, evidence that drug substance produced by this supplier (using same route of synthesis) has been approved for an existing drug product marketed in the assessor's region is considered to be sufficient evidence of acceptable risk/benefit regarding mutagenic impurities and an assessment per M7 is not required. If this is not the case, then an assessment per M7 is expected (Note needed?).

### 4.4 Alternative considerations for existing products with no changes

This guideline is not intended to be applied retrospectively to existing marketed products unless study data demonstrate genotoxicity of an impurity that was not previously considered when establishing specification. Existence of structural alerts alone is considered insufficient to trigger follow-up measures unless the impurity belongs to the "cohort of concern" structural class.

### 4.5 Considerations where an assessment is not warranted

A thorough assessment for the presence of potential mutagenic impurities is not warranted if the drug substance itself is genotoxic and therefore expected to be associated with an increased cancer risk when used clinically. If under these conditions a mutagenic impurity is known to be present in the drug substance/drug product, ICH Q3A/B would apply.

## 5. PROCESS AND PRODUCT IMPURITY ASSESSMENT

A key element in conducting a process and product risk assessment for mutagenic impurities involves an understanding of the actual and potential impurities that may be present.

As stated in the ICH Q3A/B guidance, actual and potential impurities that are likely to arise during the synthesis, purification, and storage of a new drug substance and during manufacturing and storage of a new drug product should be summarized.

Actual impurities should include those observed in the drug substance and drug product above the ICH Q3A/Q3B reporting threshold and will include degradation products. The actual degradation products are those that are observed above the ICHQ3A/Q3B reporting threshold over the shelf life of the product (drug substance and drug product) when stored at the recommended long-term storage condition in the proposed commercial packaging.

However, it is also important to understand if there are potential mutagenic impurities or degradants present below these thresholds as described below.

Potential impurities could include starting materials, reagents, and intermediates, identified impurities in starting materials and intermediates, and reasonably expected reaction by-products. Knowledge of the starting material synthesis, in particular the use of mutagenic reagents is an important factor in understanding the potential impurities in the starting materials.

Potential degradants in the drug substance and drug product are those that may be reasonably expected to form over the shelf life, but yet to be confirmed in the final packaged drug substance or drug product. Potential degradants include those above the identification threshold during accelerated stability studies (e.g. 40 °C/75% relative humidity for 6 months) and photostability studies as described in ICH Q1B. Assessment of potential degradants can be based on knowledge of known relevant degradation pathways.

All of these actual and potential impurities where the structure is known should be assessed for mutagenic potential as described in Section 6.

## 6. HAZARD ASSESSMENT ELEMENTS

Hazard assessment involves an initial analysis of actual and potential impurities by a comprehensive structure-based assessment using structure-activity relationships (SAR) (Dobo *et al.,* 2006; Mueller *et al.,* 2006; White paper reference to be added; Note 1). The focus of the structure-based assessment should be on Ames mutagenicity predictions based on the established Ames mutagenicity SAR knowledgebase. Mutagenicity assessment by Ames testing can be applied to follow up a structure-based concern to identify impurities that are DNA-reactive mutagens with carcinogenic potential.

A computational toxicology assessment should be performed using *in silico* models that predict the outcome of a Salmonella mutagenicity assay. It is recommended that an initial assessment of a chemical structure for the presence or absence of structural features associated with mutagenic potential be conducted using one of the widely-accepted *in silico* systems available. If the chemical structure in question contains an alert then this should be categorized according to the classification system published by Mueller *et al.* (2006).

For compounds that do not contain a structural alert, it is recommended that a second review step be conducted. This secondary review should consist of either one or both of the following:

1) Use of a second *in silico* system for mutagenicity prediction to ensure that no alerts are found using an alternative approach. It is recommended that this system should use a different algorithm or methodology to the initial system used in evaluating the impurity.

OR

2) Conduct database and literature searches for similar compounds that have Ames mutagenicity data that might imply that the impurity could be mutagenic or non-mutagenic.

The absence of structure-based concerns is sufficient to conclude that the impurity is of no concern, and no further action is needed with regard to mutagenicity testing.

The Ames mutagenicity test is considered sufficient to follow up on a positive structural alert and to identify a mutagenic hazard based on its historical use and high positive predictivity for DNA reactive carcinogens. An appropriately conducted negative Ames test (Note 2) would overrule any structure-based concern, and no further genotoxicity assessments would be required. These impurities should be managed and controlled as ordinary impurities according to ICH Q3A/Q3B. A positive Ames result would warrant further risk characterization and/or control measures. Alternatively adequate control measures in the case of a positive structural alert alone could be applied in place of Ames testing.

On occasion an impurity may be found to be positive in an Ames assay but levels cannot be reduced to an appropriate TTC. However, a sponsor may wish to perform additional testing in order to qualify the impurity for genotoxicity. It is recommended that an *in vitro* micronucleus assay can serve as a bridging study. Positive results in the *in vitro* micronucleus assay would trigger a combination *in vivo* bone marrow micronucleus assay and comet assay in appropriate tissues, e.g., liver and peripheral blood lymphocytes. A negative study in the *in vitro* micronucleus assay would trigger an *in vivo* gene mutation assay, e.g. *pig-a* or a transgenic mouse mutation assay. Negative results in the appropriate *in vivo* assay could qualify a bacterial mutation positive impurity.

## 7. RISK CHARACTERIZATION

### Application of compound-specific risk assessments

The existence of mechanisms leading to a dose response that is non-linear or has a threshold is increasingly recognized, not only for compounds that interact with non-DNA targets but also for DNA-reactive compounds, whose effects may be modulated by, for example, rapid detoxification before coming into contact with DNA, or by effective repair of induced damage. The regulatory approach to such compounds can be based on the identification of a critical no-observed-effect level (NOEL) and use of uncertainty factors when data are available.

Compound-specific risk assessments to derive acceptable limits should be applied instead of the TTC-based intakes where sufficient carcinogenicity data exist, or for compounds showing sufficient evidence of a threshold in the dose response. For a known mutagenic carcinogen a compound-specific acceptable limit can be calculated based on carcinogenic potency and linear extrapolation. For compounds with sufficient evidence of a threshold, calculation of permitted daily exposure (PDE) limits can apply according to ICH Q3C. Compound-specific calculations for acceptable limits can be applied case-by-case for impurities which are chemically similar to a known carcinogen compound class provided that a rationale for chemical similarity and supporting data can be demonstrated (Note needed?).

The acceptable limit derived from compound-specific calculations can be adjusted for shorter term use in the same proportions as the staged TTC approach.

## Less-than-lifetime (LTL) exposure

The TTC-based limit of 1.5 µg/day is considered to be protective for a lifetime of daily exposure. To address LTL exposures to mutagenic impurities in pharmaceuticals, an approach is applied in which the acceptable cumulative lifetime dose (1.5 µg x 25,500 days) is uniformly distributed over the total number of exposure days during LTL exposure (Felter *et al.,* 2011). This would allow higher daily intake of mutagenic impurities than would be the case for lifetime exposure and still maintain comparable risk levels for daily and non-daily treatment regimens.

When applying this concept to pharmaceuticals in early stage development of up to approximately 6 months duration, a $10^{-6}$ cancer risk level is used since these early trials often include healthy subjects for whom there is no expected health benefit. In addition, dose rate correction factors that conservatively lower the acceptable daily dose are used when treatment exposure is compressed to durations of less than 1 month. For late stage development and marketed products, adjusted TTC limits for exposure durations of greater than 6 months are based on a $10^{-5}$ cancer risk level as is the case for the default limit of 1.5 µg/day for chronic treatment (> 10 years). The following tables show acceptable daily intake values for both pre- and post-marketing products. Acceptable daily intakes during development and for marketed products are similar. While it might be assumed that acceptable risk for marketed products could be higher because of accrued benefits, more conservative acceptable daily intakes are specified because of the public health impact to large and/or non-homogeneous populations exposed to marketed products compared to populations in clinical trials.

**Table 1: Clinical Development**

| Duration of treatment | ≤ 14 days* | ≤ 1 month | > 1 – 12 months | > 1 year** |
|---|---|---|---|---|
| Daily intake [µg/day] | 120 | 120 | 20 | 10 |

*This limit would not apply to Phase I clinical trials up to 14 days where the drug substance tested negative in the Ames assay of the genotoxicity test battery.
**Phase III clinical trials are significantly less than lifetime, and the daily intake in the above table applies to all durations.

**Table 2: Marketed Products**

| Duration of treatment | ≤ 1 month | 1 - 12 months | 1 - 10 Years | >10 years |
|---|---|---|---|---|
| Daily intake [µg/day] | 120 | 20 | 10 | 1.5 |

**Exceptions and flexibility in approaches**

- Compound class specific acceptable limits higher than the default TTC can be applied based upon the recognized differences in carcinogenic potencies associated with different structural alert categories, e.g. monofunctional alkyl halides (Reference).
- Higher limits may be justified when human exposure to the impurity will be much greater from other sources e.g., food.
- Case-by-case exceptions to the use of the appropriate TTC can be justified in cases of severe disease, reduced life expectancy, or with limited therapeutic alternatives.

The TTC value should be applied to each individual impurity and multiple impurities should not be added together to meet a TTC value. This is supported by a detailed analysis of the effect of combining multiple impurities that are in similar or different chemical classes and by the conservative assumptions incorporated into the TTC and the low likelihood of synergistic carcinogenic effects at very low mutagenic impurity levels (Bercu *et al.,* 2008). This refers only up to three impurities for the 1.5 µg/day level. For less than lifetime TTC categories, the sum of all impurities should be controlled to the limits specified (Table 1, 2).

The above risk approaches are applicable to all routes of administration and no corrections to acceptable limits are generally warranted. Exceptions to consider may include situations where data justifies route-specific concerns that need to be evaluated case-by-case. These approaches are also applicable to all patient populations based upon the conservative nature of the risk approaches being applied.

## 8. CONTROL

A control strategy is a planned set of controls, derived from current product and process understanding that assures process performance and product quality (ICH Q10). A control strategy can include, but is not limited to, the following:

- Controls on material attributes (including raw materials, starting materials, intermediates, reagents, primary packaging materials)
- Controls implicit in the design of the manufacturing process
- In-process controls (including in-process tests and process parameters)
- Controls on drug substance and drug product (e.g., release testing)

When an impurity has been characterized as mutagenic, it is important to develop a control strategy that assures that the level of this impurity in the drug substance and/or drug product is below the acceptable limit. A thorough knowledge of the chemistry associated with the drug substance manufacturing process, the drug product manufacturing process, along with an understanding of the overall stability of the drug substance and drug product is fundamental to developing the appropriate controls.

There are 4 potential approaches to development of a control strategy for drug substance:

**Option 1**

- Include a test for the impurity in the drug substance specification with an acceptance criterion at or below the acceptable limit using an appropriate analytical procedure

**Option 2**

- Include a test for the impurity in the specification for a raw material, starting material or intermediate, or as an in-process control, with an acceptance criterion at or below the acceptable limit using an appropriate analytical procedure.

**Option 3**

- Include a test for the impurity in the specification for a raw material, starting material or intermediate, or as an in-process control, with an acceptance criterion above the acceptable limit using an appropriate analytical procedure coupled with demonstrated understanding of fate and purge and associated process controls that assure the level in the drug substance is below the acceptable limit without the need for any additional testing.

**Option 4**

- Understanding of process parameters and impact on residual impurity levels (including fate and purge knowledge) with sufficient confidence that the level of the impurity in the drug substance will be below the acceptable limit such that no analytical testing is needed for this impurity.

A control strategy that relies on process controls in lieu of analytical testing (Option 4) can be appropriate if scientific understanding of the chemistry and process parameters that impact levels of mutagenic impurities is understood and the risk of an impurity residing in the final drug substance or drug product above the acceptable limit is determined to be negligible. Elements of a scientific risk assessment/chemical rationale should include an assessment of various factors that influence the fate and purge of an impurity including chemical reactivity, solubility, volatility, ionizability and any physical process steps designed to remove impurities. The applicant would support this approach with analytical data when a justification based on scientific principles alone is not considered sufficient (Note needed?). Throughout the lifecycle of the product, it will be important to reassess if testing is needed when intended, or unintended changes outside of the regulatory process description, occur in the process. Process monitoring can enhance assurance of continued suitability and capability of processes to provide adequate control on the impurity.

A combination of a chemical purge argument coupled with a specification on an intermediate/starting material/raw material or an in-process control may also be appropriate if a chemistry argument alone is insufficient to conclude absence of an impurity in the final drug substance (Option 3). It is expected that monitoring at earlier stages in the synthesis would have higher limits than the levels appropriate for the final drug substance as long as the fate/purge argument for the impurity is shown to be robust and consistently produces product with impurity

levels below the acceptable limit. Where the purge factor is based on developmental data, it is important to address the expected scale-dependence or independence. A test for this impurity in the drug substance specification is not needed in this circumstance.

If Options 3 and 4 cannot be justified, then a test for the impurity on the specification for the intermediate/starting material/raw material (Option 2) or drug substance (Option 1) at the acceptable limit is recommended.

The application of 'as low as reasonably practicable' (ALARP) is not necessary if the level of the mutagenic impurity is below acceptable limits. Similarly, it is not necessary to demonstrate that alternate routes of synthesis have been explored to possibly avoid the generation of a mutagenic impurity so long as controls are in place to assure that mutagenic impurity levels do not exceed acceptable limits.

For a potential degradant that has been characterized as mutagenic, it is important to understand if the degradation pathway is relevant to the drug substance and drug product manufacturing processes and/or their proposed packaging and storage conditions. A well-designed accelerated stability study (e.g., 40 °C, 75% relative humidity, 6 months or a shorter kinetic thermal equivalent), and photostability study in the proposed packaging, with appropriate analytical procedures is recommended to determine the relevance of the potential degradation product.

Based on the result of these accelerated studies, if it is anticipated that the degradant will form at levels approaching the acceptable limit under the proposed packaging and storage conditions, then efforts to control formation of the degradant is expected. The extent of degradation can often be lowered through formulation development and/or packaging designed to protect from moisture, light, or oxygen. Monitoring for the drug substance or drug product degradant in long term primary stability studies at the proposed storage conditions (in the proposed commercial pack) will generally be expected in these cases. The determination of the need for a specification for the mutagenic degradant will generally depend on the results from these stability studies.

If it is anticipated that formulation development and packaging design options are unable to control mutagenic degradant levels to less than the acceptable limit, then a risk-benefit evaluation will be necessary to ultimately determine the appropriate control strategy.

## 9. DOCUMENTATION

Information relevant to the application of this guidance should be provided at the following stages:

**CTA (Clinical Trials)**

- For early development stages, a brief high level summary of efforts to mitigate risks of mutagenic impurities should be provided, including a short description as appropriate of the types of structures (e.g. late stage intermediates) that have been assessed to date by (Q)SAR including any structures of concern.

- For later development stages, it may be useful to demonstrate progression towards a CTD-compliant submission.

**CTD (Marketing Application)**

- Table of impurity structures assessed for (Q)SAR, the method(s) used and a summary of results and interpretation (i.e., classification). A report on the (Q)SAR methodology referenced to the white paper. There will also be situations where it is relevant to include in somewhat greater detail the (Q)SAR result. This would include compounds where the negative prediction was unexpected given the structure, cases where the prediction was superseded by expert knowledge, and equivocal situations. For compounds predicted to be Ames positive, which share an alerting structure with the drug substance, a discussion of structural features that could modulate the genotoxicity of either the impurity or the drug substance would be valuable.
- Ames test results for impurities: Regardless of the experimental outcome, a full study report would be provided in cases where an Ames assay was performed.
- Justification for acceptable limits and control strategy

## 10. NOTES

Note 1

Choosing two models that always yield the same predictions does not add value over using any one model alone. Therefore, the choice of complementary models is important. This assumes that where one program has a deficiency in identifying a positive (yields false negative) a second will complement it by predicting a true positive. The use of an expert rule-based model and a statistical-based system, the methodologies used are different by definition and there is greater likelihood of complementarity. The possibility of having predictions from two expert systems should be eliminated. This is important since expert systems, while offering low false positive rates and providing literature-based evidence for a positive prediction, do not make negative predictions and offer no measure of domain of applicability.

Note 2

To assess the mutagenic potential of impurities, a single Ames test can be carried out with a fully adequate protocol according ICH S2R and OECD 471 guidelines. The assays are expected to be performed in compliance with GLP; however, it is noted that the test article may not be prepared or analyzed in compliance with GLP regulations. Lack of full GLP compliance does not necessarily mean that the data cannot be used to support clinical trials and marketing authorizations. Such deviations should be described in the study report. The selection of Ames tester strains may be limited to those proven to be sensitive to an alert. For degradants where it is not feasible to isolate or synthesize, an Ames test can be carried out to a concentration of 250 μg/plate (Reference).

## 11. GLOSSARY

## 12. REFERENCES

Susan P Felter, Rory B Conolly, Joel P Bercu, P Michael Bolger, Alan R Boobis, Peter M J Bos, Philip Carthew, Nancy G Doerrer, Jay I Goodman, Wafa A Harrouk, David J Kirkland, Serrine S Lau, G Craig Llewellyn, R Julian Preston, Rita Schoeny, A Robert Schnatter, Angelika Tritscher, Frans van Velsen, Gary M Williams (2011). A proposed framework for assessing risk from less-than-lifetime exposures to carcinogens. Critical reviews in toxicology 41, 507-44.

## ATTACHMENTS

## APPENDICES

- Appendix A: Examples of scenarios that would trigger application of M7 Guidance

585 # Appendix A
586 # Scope Scenarios for Application of M7 Guidance
587

| Scenario | Reference to Step 1 Document Section(s) | Existing Product Approved Pre or Post ICH M7 | Applies to Drug Substance | Applies to Drug Product | Comments |
|---|---|---|---|---|---|
| Registration of new drug substances and associated drug product | 2.0 Scope/4.1 Applications for a new drug substance and associated drug product | NA | Yes | Yes | Primary intent of the M7 guidance |
| Clinical trial applications for new chemical entities and associated drug product | 2.0 Scope | NA | Yes | Yes | Identification of actual, potential and reasonably-predicted impurities will be done, but it is understood that control strategies will be less developed |
| Clinical trial applications for new drug substances for a anti-cancer drug (per ICH S9) | 2.0 Scope | NA | No | No | This scenario is out of scope of M7. |
| Clinical trial applications for new drug substances for an orphan drug | 2.0 Scope | NA | Yes | Yes | Cannot rule out orphan drugs from scope, but there may be exceptions on a case by case basis for rare diseases |
| Clinical trial application for a new drug product using an existing drug substance where no changes to the drug substance route of synthesis<br><br>Same drug substance = Same route of synthesis. | 4.2 Post approval changes - CMC changes | Post | Yes | Yes | Since drug substance was filed after the issuance of ICH M7, the control strategy will be contemporary and by default already in compliance |
| | | Pre | No | Yes | Retrospective application of the M7 guidance is not intended for existing products approved prior to the issuance of ICH M7 unless there are changes made to the synthesis or due cause for concern; new drug product would require evaluation per M7 guidance |
| Changes made to an approved drug substance synthesis | 4.2 Post approval changes – CMC | Pre | No | No | Retrospective application of the M7 guidance is not intended for existing products approved prior to the issuance of ICH M7 |

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|---|---|---|---|---|---|
| but the changes do not impact the regulatory process description (i.e. within broader established design space), that is the process change is within the regulatory process description | changes | | | | unless there are changes made to the synthesis or due cause for concern |
| | | Post | No | No | As there are no changes to the drug substance synthesis, reevaluation of the impurity control strategy is not warranted.<br><br>Risk-driven and/or periodic testing may be valuable when commercial manufacturing experience is limited or when movement within the design space may significantly alter the risk from a mutagenic impurity. |
| Changes made to an approved drug substance synthesis and the changes do impact the regulatory process description, that is the process change is not within the regulatory process description | 4.2 Post approval changes – CMC changes | Pre | Yes | No | Retrospective application of the M7 guidance is appropriate for existing drug substances if changes are made to the drug substance route of synthesis. Only the potential new or higher impurities would be evaluated<br><br>When the entire drug substance synthesis is new (e.g., first use of this drug substance supplier in this application), a section describing the risk assessment for mutagenic impurities will be needed. Evidence that this supplier's drug substance has been used in (or approved for) an existing drug marketed in one of the three ICH regions (or assessor's region) is considered to be sufficient evidence of acceptable risk/benefit regarding mutagenic impurities.<br><br>Define/focus on big changes: Trigger is the synthesis. 'Totally' new synthesis (combination of route and drug substance supplier). Weight is on applicant to demonstrate not new.<br><br>Address 'due cause for concern' scenario where new generic applicant finds new mutagenic impurity that is not covered by innovator and needs to conduct an assessment as new product. Inform innovator (i.e. retrospective)? |
| | | Post | Yes | No | Changes to the route of synthesis would trigger reevaluation of potential new or higher impurities |
| A first time generic application of an existing product where no changes | 4.2 Post approval changes - CMC changes/4.3 | Pre | No | No | Retrospective application of the M7 guidance is not intended for existing products approved prior to the issuance of ICH M7 unless there are changes made to the |

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|---|---|---|---|---|---|
| have been made to the drug substance or drug product | Special considerations for CMC changes | | | | synthesis or due cause for concern |
| | | Post | No | No | If there are no changes to the product or drug substance route of synthesis, reevaluation of mutagenic impurity risk would not be required |
| A new formulation of an approved drug substance is filed | 4.2 Post approval changes - CMC changes | Post | No | Yes | New formulation must be assessed for any new or higher degradants. Degradants that already exist in previously approved products do not require reevaluation |
| | | Pre | No | Yes | Retrospective application of the M7 guidance is not intended for existing products approved prior to the issuance of ICH M7 unless there are changes made to the synthesis or due cause for concern, or if changes are made to the formulation for which any potential new or higher degradants would be assessed |
| A product that is previously approved in a member region is filed for the first time in a different member region. The product is unchanged. | 4.2 - Post approval changes - CMC changes/4.3 Special considerations for CMC changes | Post | Yes | Yes | As there is no mutual recognition, an existing project in one member region filed for the first time in another member region would be considered a new product.<br><br>Within a member region, such as Europe, an existing product approved in one country would not be considered a new product when filed in another country and thus should not trigger application for this guidance. |
| | | Pre | No | No | Retrospective application of the M7 guidance is not intended for existing products approved prior to the issuance of ICH M7 unless there are changes made to the synthesis or due cause for concern, or if changes are made to the formulation for which any potential new or higher degradants would be assessed |
| A new supplier of the drug substance is registered. There are no changes to the existing | 4.3 Special considerations for CMC changes | Post | No | No | As long as the synthesis of the drug substance is consistent with previously approved methods, then reevaluation of mutagenic impurity risk is not necessary. The applicant would need to demonstrate that no |

| | | | | | |
|---|---|---|---|---|---|
| manufacturing process | | | | | changes have been made to a previously approved process/product |
| | | Pre | No | No | Retrospective application of the M7 guidance is not intended for existing products approved prior to the issuance of ICH M7 unless there are changes made to the synthesis or due cause for concern, or if changes are made to the formulation for which any potential new or higher degradants would be assessed. The applicant would need to demonstrate that no changes have been made to a previously approved process/product |
| An existing product (approved after the issuance of ICH M7 with higher limits based on ICH S9) associated with an advanced cancer indication is now registered for use in a non-life threatening indication | 4.2 Post approval changes – Clinical changes | Post | Yes | Yes | Since the patient population and acceptable cancer risk has changed, the previously approved impurity control strategy and limits will require reevaluation |
| An existing product is refiled for pediatric use | 4.2 Post approval changes – Clinical changes | Post | No | No | Mutagenic impurity limits are conservative and are generally applicable to all patient groups. There may be some exceptions however. |
| | | Pre | No | No | Retrospective application of the M7 guidance is not intended for existing products approved prior to the issuance of ICH M7 unless there are changes made to the synthesis or due cause for concern, or if changes are made to the formulation for which any potential new or higher degradants would be assessed |
| An existing product is refiled for a different indication | 4.2 Post approval changes – Clinical | Post | No | No | Assuming no change in the acceptable cancer risk, then reevaluation is not necessary<br><br>Note: True if control was to general TTC; if higher for earlier indication, then will need to |

| | | | | | |
|---|---|---|---|---|---|
| | changes | | | | re-evaluate. |
| | | Pre | No | No | Retrospective application of the M7 guidance is not intended for existing products approved prior to the issuance of ICH M7 unless there are changes made to the synthesis or due cause for concern, or if changes are made to the formulation for which any potential new or higher degradants would be assessed |
| An existing product is refiled with a higher dose resulting in increased daily exposure | 4.2 Post approval changes – Clinical changes | Post | yes | Yes | The impurity/degradant limits would require reevaluation in the context of the increased dose. |
| | | Pre | No | Yes/No | Retrospective application of the M7 guidance to existing products is not intended unless there are new or higher levels of existing impurities. As the drug substance is unchanged, reevaluation would not be required. If the dose change was associated with a new formulation, then application of M7 guidance to the drug product would be required. If the dose increase did not involve a formulation change, then application of the guidance would not be required. |
| New combination product is filed that contains one new drug substance and an existing drug substance (no changes to the manufacturing process) | 4.1 Applications for a new drug substance and associated drug product/ 4.2 Post approval changes | Pre | Yes (new drug substance)<br><br>No (existing drug substance) | Yes | M7 guidance would apply to the new drug substance. For the existing drug substance, retrospective application of M7 guidance to existing products is not intended. For the drug product, this would classify as a new drug product so the guidance would apply to any new or higher levels of degradants |

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# ICH M7 ステップ 1 文書
# (2011 年 11 月 15 日、Sevilla 作業部会ミーテイング)

# 潜在的な発がんリスクの制限を目的とした
# 医薬品中の DNA 反応性（変異原性）不純物の評価および管理

## 1. はじめに

原薬の合成では、反応性の化学物質、溶媒、触媒、その他の補助物質が使用される。化学合成やその後の分解の結果、微量の不純物がすべての原薬および関連製剤に残留する。ほとんどの不純物の安全性確認および管理については、ICH Q3A (R2)：「新有効成分含有医薬品のうち原薬の不純物に関するガイドライン」および Q3B (R2)：「新有効成分含有医薬品のうち製剤の不純物に関するガイドライン」で指針が与えられているが、DNA 反応性不純物についての指針はこれまでほとんど提供されていない。本ガイダンスでは、潜在的な発がんリスクの制限を目的として、こうした変異原性を有する不純物の構造決定、分類、安全性確認、管理に適用される実用的な枠組みを提供する。本ガイダンスは、ICH Q3A (R2)、Q3B (R2)（要注釈？）および ICH M3 (R2)：「医薬品の臨床試験および製造販売承認申請のための非臨床安全性試験の実施についてのガイダンス」を補完するものである。

本ガイダンスでは、変異原性不純物の濃度を発がんリスクが非常に低いと考えられる低濃度で確立するにあたって、安全性と品質リスクマネジメントの両方の検討事項が強調される。最終的に得られた原薬／製剤に残留する（または残留が予想される）変異原性不純物の推奨される評価法と管理法について、意図されているヒトへの使用条件を考慮して、概略を述べる。

## 2. ガイドラインの適用範囲

本文書は、開発中の新規原薬の新薬治験許可申請と販売承認申請中および市販後の関連製剤について、開発企業に指針を提供することを目的としている。また既存の承認についても、原薬合成に関する変更の結果、新たな不純物が生じる可能性または既存の不純物が以前より高濃度で生じる可能性について評価が必要な場合には、本ガイダンスが適用される。また、製剤処方の変更の結果、新たな分解物が生じる可能性または既存の分解物が以前より高濃度で生じる可能性について評価が必要となる場合にも、そうした変更と関連した新規申請に適用できる。さらに、既に承認された製剤を新たな適応、患者集団、用法・用量に関して新規申請する場合にも、それらの変更ががんリスクに著しい影響を与える場合に適用される。

このガイダンスは次のような種類の原薬や製剤には適用されない（ICH Q3A/B）：

- 生物学的／バイオテクノロジー応用

43 ・ ペプチド
44 ・ オリゴヌクレオチド
45 ・ 放射性医薬品
46 ・ 醗酵製剤
47 ・ 生薬製剤
48 ・ 動物または植物由来の生薬製剤
49
50 これらの製剤が化学修飾され（有機化学的リンカーの付加、半合成製剤など）、関連の
51 有機化学的不純物を評価する可能性がある場合は特に例外とする。
52
53 本ガイダンスは ICH S9 で述べられているように、進行がんの治療薬には適用されない。
54 また、原薬それ自体が遺伝毒性を有する製剤に対しても適用されない。これらの場合、
55 変異原性を有する不純物は通常の不純物として、ICH Q3A/B にしたがって管理するこ
56 と。
57
58 このガイダンスは市販製剤に既に使用されている添加物中の不純物や、これらの添加物
59 に関連した製法変更には適用されない。このガイダンスは製剤に初めて使用される新し
60 い添加物には適用される（要注釈？）。
61
62 製剤の包装に関連する溶出物は本ガイダンスの適用対象ではないが、本ガイダンスで示
63 す発がんリスク制限のための安全性評価の原則は、必要であれば適用可能である。
64
65
66 **3. 一般原則**
67
68 本ガイダンスの文脈において、ある化合物（不純物）が遺伝毒性物質に分類されるとい
69 うことは、一般に、*in vitro* および／または *in vivo* の適切な遺伝毒性試験で陽性結果が
70 得られていることを意味する。本ガイダンスで焦点を当てる化合物は、低レベルで
71 DNA に直接損傷を与え変異を引き起こす可能性があり、それによってがんを誘発する
72 可能性がある DNA 反応性物質である。このタイプの変異原性発がん物質の検出には、
73 通常、微生物を使用した復帰突然変異試験（Ames 試験）が使用される。この試験で陰
74 性の結果が示された遺伝毒性物質は通常、閾値メカニズムを有しており、不純物として
75 の通常の濃度では普通、ヒトでの発がんリスクはない（Kirkland *et al.*, 追加参考文献）。
76 したがって、変異原性不純物によって生じる可能性があるヒトでのがんリスクを制限す
77 る目的のためには、Ames 試験を使用し、不純物の変異原性の可能性／変異原性および
78 その管理の必要性を検討する。構造ベースの評価を実施し、既存の知識ベースに基づい
79 て Ames 試験の結果を予測することは有益である。この評価を行うためには、文献レビ
80 ュー、専門家知識の利用および／または毒性の計算科学的評価など、様々な方法がある。
81
82 試験されていない化学物質に関して、発がん性などの毒性を示さない共通の用量を定義
83 するため、「毒性の懸念が生じる閾値（threshold of toxicological concern; TTC）」と呼
84 ばれる概念が提唱された（Munro *et al.* 1999, Kroes and Kozianowski 2002）。変異原性不