ICH M7(R2) Guideline on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk

Step 5

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1. Introduction

The synthesis of drug substances involves the use of reactive chemicals, reagents, solvents, catalysts, and other processing aids. As a result of chemical synthesis or subsequent degradation, 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 (Ref. 1, 2) provides guidance for qualification and control for the majority of the impurities, limited guidance is provided for those impurities that are DNA reactive. The purpose of this guideline is to provide a practical framework that is applicable to the identification, categorization, qualification, and control of these mutagenic impurities to limit potential carcinogenic risk. This guideline is intended to complement ICH Q3A(R2), Q3B(R2) (Note 1), and ICH M3(R2): Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorizations for Pharmaceuticals (Ref. 3).

This guideline emphasizes considerations of both safety and quality risk management in establishing levels of mutagenic impurities that are expected to pose negligible 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 new drug substances and new drug products during their clinical development and subsequent applications for marketing. It also applies to post-approval submissions of marketed products, and to new marketing applications for products with a drug substance that is present in a previously approved product, in both cases only where:

- Changes to the drug substance synthesis result in new impurities or increased acceptance criteria for existing impurities;

- Changes in the formulation, composition or manufacturing process result in new degradation products or increased acceptance criteria for existing degradation products;

- Changes in indication or dosing regimen are made which significantly affect the acceptable cancer risk level.

Assessment of the mutagenic potential of impurities as described in this guideline is not intended for the following types of drug substances and drug products: biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation products, herbal products, and crude products of animal or plant origin.

This guideline does not apply to drug substances and drug products intended for advanced cancer indications as defined in the scope of ICH S9 (Ref. 4). Additionally, there may be some cases where a drug substance intended for other indications is itself genotoxic at therapeutic concentrations and may be expected to be associated with an increased cancer risk. Exposure to a mutagenic impurity in these cases would not significantly add to the cancer risk of the drug substance. Therefore, impurities could be controlled at acceptable levels for non-mutagenic impurities.

Assessment of the mutagenic potential of impurities as described in this guideline is not intended for excipients used in existing marketed products, flavoring agents, colorants, and perfumes. Application of this guideline to leachables associated with drug product packaging is not intended, but the safety risk assessment principles outlined in this guideline for limiting potential carcinogenic risk can be used if warranted. The safety risk assessment principles of this guideline can be used if warranted for

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impurities in excipients that are used for the first time in a drug product and are chemically synthesized.

3. General principles

The focus of this guideline 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 (mutagenicity) assay. Other types of genotoxicants that are non-mutagenic typically have threshold mechanisms and usually do not pose carcinogenic risk in humans at the level ordinarily present as impurities. Therefore to limit a possible human cancer risk associated with the exposure to potentially mutagenic impurities, the bacterial mutagenicity assay is used to assess the mutagenic potential and the need for controls. Structure-based assessments are useful for predicting bacterial mutagenicity outcomes based upon the established knowledge. There are a variety of approaches to conduct this evaluation including a review of the available literature, and/or computational toxicology assessment.

A Threshold of Toxicological Concern (TTC) concept was developed to define an acceptable intake for any unstudied chemical that poses a negligible risk of carcinogenicity or other toxic effects. The methods upon which the TTC is based are generally considered to be very conservative since they involve a simple linear extrapolation from the dose giving a 50% tumor incidence (TD50) to a 1 in 106 incidence, using TD50 data for the most sensitive species and most sensitive site of tumor induction. For application of a TTC in the assessment of acceptable limits of mutagenic impurities in drug substances and drug products, a value of 1.5 µg/day corresponding to a theoretical 10-5 excess lifetime risk of cancer, can be justified. Some structural groups were identified to be of such high potency that intakes even below the TTC would theoretically be associated with a potential for a significant carcinogenic risk. This group of high potency mutagenic carcinogens referred to as the "cohort of concern", comprises aflatoxin-like-, N-nitroso-, and alkyl-azoxy compounds.

During clinical development, it is expected that control strategies and approaches will be less developed in earlier phases where overall development experience is limited. This guideline bases acceptable intakes for mutagenic impurities on established risk assessment strategies. Acceptable risk during the early development phase is set at a theoretically calculated level of approximately one additional cancer per million. For later stages in development and for marketed products, acceptable increased cancer risk is set at a theoretically calculated level of 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 greater than 1 in 3. It is noted that established cancer risk assessments are based on lifetime exposures. Less-Than-Lifetime (LTL) exposures both during development and marketing can have higher acceptable intakes of impurities and still maintain comparable risk levels. The use of a numerical cancer risk value (1 in 100,000) and its translation into risk-based doses (TTC) is a highly hypothetical concept that should not be regarded as a realistic indication of the actual risk. Nevertheless, the TTC concept provides an estimate of safe exposures for any mutagenic compound. However, exceeding the TTC is not necessarily associated with an increased cancer risk given the conservative assumptions employed in the derivation of the TTC value. The most likely increase in cancer incidence is actually much less than 1 in 100,000. In addition, in cases where a mutagenic compound is a non-carcinogen in a rodent bioassay, there would be no predicted increase in cancer risk. Based on all the above considerations, any exposure to an impurity that is later identified as a mutagen is not necessarily associated with an increased cancer risk for patients already exposed to the impurity. A risk assessment would determine whether any further actions would be taken.

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

There may be cases when an impurity is also a metabolite of the drug substance. In such cases the risk assessment that addresses mutagenicity of the metabolite can qualify the impurity.

4. Considerations for marketed products

This guideline is not intended to be applied retrospectively (i.e., to products marketed prior to adoption of this guideline). However, some types of post-approval changes warrant a reassessment of safety relative to mutagenic impurities. This section applies to these post- approval changes for products marketed prior to, or after, the adoption of this guideline. Section 8.5 (Lifecycle Management) contains additional recommendations for products marketed after adoption of this guideline.

4.1. Post-Approval Changes to the Drug Substance Chemistry, Manufacturing, and Controls

Post-approval submissions involving the drug substance chemistry, manufacturing, and controls should include an evaluation of the potential risk impact associated with mutagenic impurities from changes to the route of synthesis, reagents, solvents, or process conditions after the starting material. Specifically, changes should be evaluated to determine if the changes result in any new mutagenic impurities or higher acceptance criteria for existing mutagenic impurities. Reevaluation of impurities not impacted by changes is not recommended. For example, when only a portion of the manufacturing process is changed, the assessment of risk from mutagenic impurities should be limited to whether any new mutagenic impurities result from the change, whether any mutagenic impurities formed during the affected step are increased, and whether any known mutagenic impurities from up-stream steps are increased. Regulatory submissions associated with such changes should describe the assessment as outlined in Section 9.2. Changing the site of manufacture of drug substance, intermediates, or starting materials or changing raw materials supplier will not require a reassessment of mutagenic impurity risk.

When a new drug substance supplier is proposed, evidence that the drug substance produced by this supplier using the same route of synthesis as 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 this guideline is not required. If this is not the case, then an assessment per this guideline is expected.

4.2. Post-Approval Changes to the Drug Product Chemistry, Manufacturing, and Controls

Post-approval submissions involving the drug product (e.g., change in composition, manufacturing process, dosage form) should include an evaluation of the potential risk associated with any new mutagenic degradation products or higher acceptance criteria for existing mutagenic degradation products. If appropriate, the regulatory submission would include an updated control strategy. Reevaluation of the drug substance associated with drug products is not recommended or expected provided there are no changes to the drug substance. Changing the site of manufacture of drug product will not require a reassessment of mutagenic impurity risk.

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4.3. Changes to the Clinical Use of Marketed Products

Changes to the clinical use of marketed products that can warrant a reevaluation of the mutagenic impurity limits include a significant increase in clinical dose, an increase in duration of use (in particular when a mutagenic impurity was controlled above the lifetime acceptable intake for a previous indication that may no longer be appropriate for the longer treatment duration associated with the new indication), or for a change in indication from a serious or life threatening condition where higher acceptable intakes were justified (Section 7.5) to an indication for a less serious condition where the existing impurity acceptable intakes may no longer be appropriate. Changes to the clinical use of marketed products associated with new routes of administration or expansion into patient populations that include pregnant women and/or pediatrics will not warrant a reevaluation, assuming no increases in daily dose or duration of treatment.

4.4. Other Considerations for Marketed Products

Application of this guideline may be warranted to marketed products if there is specific cause for concern. The existence of impurity structural alerts alone is considered insufficient to trigger follow-up measures, unless it is a structure in the cohort of concern (Section 3). However, a specific cause for concern would be new relevant impurity hazard data (classified as Class 1 or 2, Section 6) generated after the overall control strategy and specifications for market authorization were established. This new relevant impurity hazard data should be derived from high-quality scientific studies consistent with relevant regulatory testing guidelines, with data records or reports readily available. Similarly, a newly discovered impurity that is a known Class 1 or Class 2 mutagen that is present in a marketed product could also be a cause for concern. In both of these cases when the applicant becomes aware of this new information, an evaluation per this guideline should be conducted.

5. Drug substance and drug product impurity assessment

Actual and potential impurities that are likely to arise during the synthesis and storage of a new drug substance, and during manufacturing and storage of a new drug product should be assessed.

The impurity assessment is a two-stage process:

- Actual impurities that have been identified should be considered for their mutagenic potential.

- An assessment of potential impurities likely to be present in the final drug substance is carried out to determine if further evaluation of their mutagenic potential is required.

The steps as applied to synthetic impurities and degradation products are described in Sections 5.1 and 5.2, respectively.

5.1. Synthetic Impurities

Actual impurities include those observed in the drug substance above the ICH Q3A reporting thresholds. Identification of actual impurities is expected when the levels exceed the identification thresholds outlined by ICH Q3A. It is acknowledged that some impurities below the identification threshold may also have been identified.

Potential impurities in the drug substance can include starting materials, reagents and intermediates in the route of synthesis from the starting material to the drug substance.

The risk of carryover into the drug substance should be assessed for identified impurities that are present in starting materials and intermediates, and impurities that are reasonably expected by-products in the route of synthesis from the starting material to the drug substance. As the risk of

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carryover may be negligible for some impurities (e.g., those impurities in early synthetic steps of long routes of synthesis), a risk-based justification could be provided for the point in the synthesis after which these types of impurities should be evaluated for mutagenic potential.

For starting materials that are introduced late in the synthesis of the drug substance (and where the synthetic route of the starting material is known) the final steps of the starting material synthesis should be evaluated for potential mutagenic impurities.

Actual impurities where the structures are known and potential impurities as defined above should be evaluated for mutagenic potential as described in Section 6.

5.2. Degradation Products

Actual drug substance degradation products include those observed above the ICH Q3A reporting threshold during storage of the drug substance in the proposed long-term storage conditions and primary and secondary packaging. Actual degradation products in the drug product include those observed above the ICH Q3B reporting threshold during storage of the drug product in the proposed long-term storage conditions and primary and secondary packaging, and also include those impurities that arise during the manufacture of the drug product. Identification of actual degradation products is expected when the levels exceed the identification thresholds outlined by ICH Q3A/Q3B. It is acknowledged that some degradation products below the identification threshold may also have been identified.

Potential degradation products in the drug substance and drug product are those that may be reasonably expected to form during long term storage conditions. Potential degradation products include those that form above the ICH Q3A/B identification threshold during accelerated stability studies (e.g., 40°C/75% relative humidity for 6 months) and confirmatory photo-stability studies as described in ICH Q1B (Ref. 5), but are yet to be confirmed in the drug substance or drug product under long-term storage conditions in the primary packaging.

Knowledge of relevant degradation pathways can be used to help guide decisions on the selection of potential degradation products to be evaluated for mutagenicity e.g., from degradation chemistry principles, relevant stress testing studies, and development stability studies.

Actual and potential degradation products likely to be present in the final drug substance or drug product and where the structure is known should be evaluated for mutagenic potential as described in Section

5.3. Considerations for Clinical Development

It is expected that the impurity assessment described in Sections 5.1 and 5.2 applies to products in clinical development. However, it is acknowledged that the available information is limited. For example, information from long term stability studies and photo-stability studies may not be available during clinical development and thus information on potential degradation products may be limited. Additionally, the thresholds outlined in ICH Q3A/B do not apply to products in clinical development and consequently fewer impurities will be identified.

6. Hazard assessment elements

Hazard assessment involves an initial analysis of actual and potential impurities by conducting database and literature searches for carcinogenicity and bacterial mutagenicity data in order to classify them as Class 1, 2, or 5 according to Table 1. If data for such a classification are not available, an

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assessment of Structure-Activity Relationships (SAR) that focuses on bacterial mutagenicity predictions should be performed. This could lead to a classification into Class 3, 4, or 5.

Table 1: Impurities Classification with Respect to Mutagenic and Carcinogenic Potential and Resulting Control Actions

Class	Definition	Proposed action for control (details in Section 7 and 8)
1	Known mutagenic carcinogens	Control at or below compound- specific acceptable limit
2	Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive*, no rodent carcinogenicity data)	Control at or below acceptable limits (appropriate TTC)
3	Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data	Control at or below acceptable limits (appropriate TTC) or conduct bacterial mutagenicity assay; If non-mutagenic = Class 5 If mutagenic = Class 2
4	Alerting structure, same alert in drug substance or compounds related to the drug substance (e.g., process intermediates) which have been tested and are non- mutagenic	Treat as non-mutagenic impurity
5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity	Treat as non-mutagenic impurity

*Or other relevant positive mutagenicity data indicative of DNA-reactivity related induction of gene mutations (e.g., positive findings in in vivo gene mutation studies)

A computational toxicology assessment should be performed using (Q)SAR methodologies that predict the outcome of a bacterial mutagenicity assay (Ref. 6). Two (Q)SAR prediction methodologies that complement each other should be applied. One methodology should be expert rule-based and the second methodology should be statistical-based. (Q)SAR models utilizing these prediction methodologies should follow the general validation principles set forth by the Organisation for Economic Co-operation and Development (OECD).

The absence of structural alerts from two complementary (Q)SAR methodologies (expert rule- based and statistical) is sufficient to conclude that the impurity is of no mutagenic concern, and no further testing is recommended (Class 5 in Table 1).

If warranted, the outcome of any computer system-based analysis can be reviewed with the use of expert knowledge in order to provide additional supportive evidence on relevance of any positive, negative, conflicting or inconclusive prediction and provide a rationale to support the final conclusion.

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To follow up on a relevant structural alert (Class 3 in Table 1), either adequate control measures could be applied or a bacterial mutagenicity assay with the impurity alone can be conducted. An appropriately conducted negative bacterial mutagenicity assay (Note 2) would overrule any structure-based concern, and no further genotoxicity assessments would be recommended (Note 1). These impurities should be considered non-mutagenic (Class 5 in Table 1). A positive bacterial mutagenicity result would warrant further hazard assessment and/or control measures (Class 2 in Table 1). For instance, when levels of the impurity cannot be controlled at an appropriate acceptable limit, it is recommended that the impurity be tested in an in vivo gene mutation assay in order to understand the relevance of the bacterial mutagenicity assay result under in vivo conditions. The selection of other in vivo genotoxicity assays should be scientifically justified based on knowledge of the mechanism of action of the impurity and expected target tissue exposure (Note 3). In vivo studies should be designed taking into consideration existing ICH genotoxicity Guidelines. Results in the appropriate in vivo assay may support setting compound specific impurity limits.

An impurity with a structural alert that is shared (e.g., same structural alert in the same position and chemical environment) with the drug substance or related compounds can be considered as non-mutagenic (Class 4 in Table 1) if the testing of such material in the bacterial mutagenicity assay was negative.

7. Risk characterization

As a result of hazard assessment described in Section 6, each impurity will be assigned to one of the five classes in Table 1. For impurities belonging in Classes 1, 2, and 3 the principles of risk characterization used to derive acceptable intakes are described in this section.

7.1. TTC-based Acceptable Intakes

A TTC-based acceptable intake of a mutagenic impurity of 1.5 μg per person per day is considered to be associated with a negligible risk (theoretical excess cancer risk of <1 in 100,000 over a lifetime of exposure) and can in general be used for most pharmaceuticals as a default to derive an acceptable limit for control. This approach would usually be used for mutagenic impurities present in pharmaceuticals for long-term treatment (> 10 years) and where no carcinogenicity data are available (Classes 2 and 3).

7.2. Acceptable Intakes Based on Compound-Specific Risk Assessments

7.2.1. Mutagenic Impurities with Positive Carcinogenicity Data (Class 1 in Table 1)

Compound-specific risk assessments to derive acceptable intakes should be applied instead of the TTC-based acceptable intakes where sufficient carcinogenicity data exist. For a known mutagenic carcinogen, a compound-specific acceptable intake can be calculated based on carcinogenic potency and linear extrapolation as a default approach. Alternatively, other established risk assessment practices such as those used by international regulatory bodies may be applied either to calculate acceptable intakes or to use already existing values published by regulatory authorities (Note 4).

Compound-specific calculations for acceptable intakes can be applied case-by-case for impurities which are chemically similar to a known carcinogen compound class (class-specific acceptable intakes) provided that a rationale for chemical similarity and supporting data can be demonstrated (Note 5).

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7.2.2. Mutagenic Impurities with Evidence for a Practical Threshold

The existence of mechanisms leading to a dose response that is non-linear or has a practical 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 No-Observed Effect Level (NOEL) and use of uncertainty factors (ICH Q3C(R5), Ref. 7) to calculate a Permissible Daily Exposure (PDE) when data are available.

The acceptable intakes derived from compound-specific risk assessments (Section 7.2) can be adjusted for shorter duration of use in the same proportions as defined in the following sections (Section 7.3.1 and 7.3.2) or should be limited to not more than 0.5%, whichever is lower. For example, if the compound specific acceptable intake is 15 µg/day for lifetime exposure, the less than lifetime limits (Table 2) can be increased to a daily intake of 100 µg (> 1-10 years treatment duration), 200 µg (> 1-12 months) or 1200 µg (< 1 month). However, for a drug with a maximum daily dose of, for instance, 100 mg the acceptable daily intake for the < 1 month duration would be limited to 0.5% (500 µg) rather than 1200 µg.

7.3. Acceptable Intakes in Relation to LTL Exposure

Standard risk assessments of known carcinogens assume that cancer risk increases as a function of cumulative dose. Thus, cancer risk of a continuous low dose over a lifetime would be equivalent to the cancer risk associated with an identical cumulative exposure averaged over a shorter duration.

The TTC-based acceptable intake 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/day x 25,550 days = 38.3 mg) is uniformly distributed over the total number of exposure days during LTL exposure. 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. Table 2 is derived from the above concepts and illustrates the acceptable intakes for LTL to lifetime exposures for clinical development and marketing. In the case of intermittent dosing, the acceptable daily intake should be based on the total number of dosing days instead of the time interval over which the doses were administered and that number of dosing days should be related to the relevant duration category in Table 2. For example, a drug administered once per week for 2 years (i.e., 104 dosing days) would have an acceptable intake per dose of 20µg.

Table 2: Acceptable Intakes for an Individual Impurity

Duration of treatment	$\leq$ 1 month	>1 - 12 months	>1 - 10 Years	>10 years to lifetime
Daily intake [µg/day]	120	20	10	1.5

7.3.1. Clinical Development

Using this LTL concept, acceptable intakes of mutagenic impurities are recommended for limited treatment periods during clinical development of up to 1 month, 1 to 12 months and more than one year up to completion of Phase 3 clinical trials (Table 2). These adjusted acceptable intake values maintain a 10-6 risk level in early clinical development when benefit has not yet been established and a 10-5 risk level for later stages in development (Note 6).

An alternative approach to the strict use of an adjusted acceptable intake for any mutagenic impurity could be applied for Phase 1 clinical trials for dosing up to 14 days. For this approach, only impurities that are known mutagenic carcinogens (Class 1) and known mutagens of unknown carcinogenic potential (Class 2), as well as impurities in the cohort of concern chemical class, should be controlled (see Section 8) to acceptable limits as described in Section 7. All other impurities would be treated as non-mutagenic impurities. This includes impurities which contain structural alerts (Class 3), which alone would not trigger action for an assessment for this limited Phase 1 duration.

7.3.2. Marketed Products

The treatment duration categories with acceptable intakes in Table 2 for marketed products are intended to be applied to anticipated exposure durations for the great majority of patients. The proposed intakes along with various scenarios for applying those intakes are described in Table 4, Note 7. In some cases, a subset of the population of patients may extend treatment beyond the marketed drugs categorical upper limit (e.g., treatment exceeding 10 years for an acceptable intake of 10 µg/day, perhaps receiving 15 years of treatment). This would result in a negligible increase (in the example given, a fractional increase to 1.5/100,000) compared to the overall calculated risk for the majority of patients treated for 10 years.

7.4. Acceptable Intakes for Multiple Mutagenic Impurities

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

For combination products each active ingredient should be regulated separately.

Table 3: Acceptable Total Daily Intakes for Multiple Impurities

Duration of treatment	< 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Total Daily intake [µg/day]	120	60	30	5

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

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7.5. Exceptions and Flexibility in Approaches

- Higher acceptable intakes may be justified when human exposure to the impurity will be much greater from other sources e.g., food, or endogenous metabolism (e.g., formaldehyde).

- Case-by-case exceptions to the use of the appropriate acceptable intake can be justified in cases of severe disease, reduced life expectancy, late onset but chronic disease, or with limited therapeutic alternatives.

- Compounds from some structural classes of mutagens can display extremely high carcinogenic potency (cohort of concern), i.e., aflatoxin-like-, N-nitroso-, and alkyl- azoxy structures. If these compounds are found as impurities in pharmaceuticals, acceptable intakes for these high-potency carcinogens would likely be significantly lower than the acceptable intakes defined in this guideline. Although the principles of this guideline can be used, a case-by-case approach using e.g., carcinogenicity data from closely related structures, if available, should usually be developed to justify acceptable intakes for pharmaceutical development and marketed products.

The above risk approaches described in Section 7 are applicable to all routes of administration and no corrections to acceptable intakes are generally warranted. Exceptions to consider may include situations where data justify route-specific concerns that should 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, Ref. 8). A control strategy can include, but is not limited to, the following:

- Controls on material attributes (including raw materials, starting materials, intermediates, reagents, solvents, primary packaging materials);

- Facility and equipment operating conditions;

- 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 Classes 1, 2, or 3 in Table 1, it is important to develop a control strategy that assures that the level of this impurity in the drug substance and drug product is below the acceptable limit. A thorough knowledge of the chemistry associated with the drug substance manufacturing process, and of 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. Developing a strategy to control mutagenic impurities in the drug product is consistent with risk management processes identified in ICH Q9 (Ref. 9). A control strategy that is based on product and process understanding and utilisation of risk management principles will lead to a combination of process design and control and appropriate analytical testing, which can also provide an opportunity to shift controls upstream and minimize the need for end-product testing.

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8.1. Control of Process Related Impurities

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.

For an Option 1 control approach, it is possible to apply periodic verification testing per ICH Q6A (Ref. 10). Periodic verification testing is justified when it can be shown that levels of the mutagenic impurity in the drug substance are less than 30% of the acceptable limit for at least 6 consecutive pilot scale or 3 consecutive production scale batches. If this condition is not fulfilled, a routine test in the drug substance specification is recommended. See Section 8.3 for additional considerations.

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 of the impurity in the drug substance, 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 later in the process.

This option can be justified when the level of the impurity in the drug substance will be less than 30% of the acceptable limit by review of data from laboratory scale experiments (spiking experiments are encouraged) and where necessary supported by data from pilot scale or commercial scale batches. See Case Examples 1 and 2. Alternative approaches can be used to justify Option 3.

Option 4

Understand 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 recommended for this impurity. (i.e., the impurity does not need to be listed on any specification).

A control strategy that relies on process controls in lieu of analytical testing can be appropriate if the process chemistry and process parameters that impact levels of mutagenic impurities are understood and the risk of an impurity residing in the final drug substance above the acceptable limit is determined to be negligible. In many cases justification of this control approach based on scientific principles alone is sufficient. Elements of a scientific risk assessment can be used to justify an option 4 approach. The risk assessment can be based on physicochemical properties and process 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 result of this risk assessment might be shown as an estimated purge factor for clearance of the impurity by the process (Ref. 11).

Option 4 is especially useful for those impurities that are inherently unstable (e.g., thionyl chloride that reacts rapidly and completely with water) or for those impurities that are introduced early in the synthesis and are effectively purged.

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In some cases an Option 4 approach can be appropriate when the impurity is known to form, or is introduced late in the synthesis, however process-specific data should then be provided to justify this approach.

8.2. Considerations for Control Approaches

For Option 4 approaches where justification based on scientific principles alone is not considered sufficient, as well as for Option 3 approaches, analytical data to support the control approach is expected. This could include as appropriate information on the structural changes to the impurity caused by downstream chemistry ("fate"), analytical data on pilot scale batches, and in some cases, laboratory scale studies with intentional addition of the impurity ("spiking studies"). In these cases, it is important to demonstrate that the fate/purge argument for the impurity is robust and will consistently assure a negligible probability of an impurity residing in the final drug substance above the acceptable limit. Where the purge factor is based on developmental data, it is important to address the expected scale-dependence or independence. In the case that the small scale model used in the development stage is considered to not represent the commercial scale, confirmation of suitable control in pilot scale and/or initial commercial batches is generally appropriate. The need for data from pilot/commercial batches is influenced by the magnitude of the purge factor calculated from laboratory or pilot scale data, point of entry of the impurity, and knowledge of downstream process purge points.

If Options 3 and 4 cannot be justified, then a test for the impurity on the specification for a raw material, starting material or intermediate, or as an in-process control (Option 2) or drug substance (Option 1) at the acceptable limit should be included. For impurities introduced in the last synthetic step, an Option 1 control approach would be expected unless otherwise justified.

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.

In cases where control efforts cannot reduce the level of the mutagenic impurity to below the acceptable limit and levels are ALARP, a higher limit may be justified based on a risk/benefit analysis.

8.3. Considerations for Periodic Testing

The above options include situations where a test is recommended to be included in the specification, but where routine measurement for release of every batch may not be necessary. This approach, referred to as periodic or skip testing in ICH Q6A could also be called "Periodic Verification Testing." This approach may be appropriate when it can be demonstrated that processing subsequent to impurity formation/introduction clears the impurity. It should be noted that allowance of Periodic Verification Testing is contingent upon use of a process that is under a state of control (i.e., produces a quality product that consistently meets specifications and conforms to an appropriately established facility, equipment, processing, and operational control regimen). If upon testing, the level of the mutagenic impurity fails to meet the acceptance criteria established for the periodic test, the drug producer should immediately commence full testing (i.e., testing of every batch for the attribute specified) until the cause of the failure has been conclusively determined, corrective action has been implemented, and the process is again documented to be in a state of control. As noted in ICH Q6A, regulatory authorities should be notified of a periodic verification test failure to evaluate the risk/benefit of previously released batches that were not tested.

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8.4. Control of Degradation Products

For a potential degradation product 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) in the proposed packaging, with appropriate analytical procedures is recommended to determine the relevance of the potential degradation product. Alternatively, well designed kinetically equivalent shorter term stability studies at higher temperatures in the proposed commercial package may be used to determine the relevance of the degradation pathway prior to initiating longer term stability studies. This type of study would be especially useful to understand the relevance of those potential degradation products that are based on knowledge of potential degradation pathways but not yet observed in the product.

Based on the result of these accelerated studies, if it is anticipated that the degradation product will form at levels approaching the acceptable limit under the proposed packaging and storage conditions, then efforts to control formation of the degradation product is expected. In these cases, monitoring for the drug substance or drug product degradation product in long term primary stability studies at the proposed storage conditions (in the proposed commercial pack) is expected unless otherwise justified. Whether or not a specification limit for the mutagenic degradation product is appropriate 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 degradation product levels to less than the acceptable limit and levels are as low as reasonably practicable, a higher limit can be justified based on a risk/benefit analysis.

8.5. Lifecycle Management

This section is intended to apply to those products approved after the issuance of this guideline.

The quality system elements and management responsibilities described in ICH Q10 are intended to encourage the use of science-based and risk-based approaches at each lifecycle stage, thereby promoting continual improvement across the entire product lifecycle. Product and process knowledge should be managed from development through the commercial life of the product up to and including product discontinuation.

The development and improvement of a drug substance or drug product manufacturing process usually continues over its lifecycle. Manufacturing process performance, including the effectiveness of the control strategy, should be periodically evaluated. Knowledge gained from commercial manufacturing can be used to further improve process understanding and process performance and to adjust the control strategy.

Any proposed change to the manufacturing process should be evaluated for the impact on the quality of drug substance and drug product. This evaluation should be based on understanding of the manufacturing process and should determine if appropriate testing to analyze the impact of the proposed changes is required. Additionally, improvements in analytical procedures may lead to structural identification of an impurity. In those cases the new structure would be assessed for mutagenicity as described in this guideline.

Throughout the lifecycle of the product, it will be important to reassess if testing is recommended when intended or unintended changes occur in the process. This applies when there is no routine monitoring at the acceptable limit (Option 3 or Option 4 control approaches), or when applying periodic rather than batch-by-batch testing. This testing should be performed at an appropriate point in the manufacturing process.

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In some cases, the use of statistical process control and trending of process measurements can be useful for continued suitability and capability of processes to provide adequate control on the impurity. Statistical process control can be based on process parameters that influence impurity formation or clearance, even when that impurity is not routinely monitored (e.g., Option 4).

All changes should be subject to internal change management processes as part of the quality system (ICH Q10). Changes to information filed and approved in a dossier should be reported to regulatory authorities in accordance with regional regulations and guidelines.

8.6. Considerations for Clinical Development

It is recognized that product and process knowledge increases over the course of development and therefore it is expected that data to support control strategies in the clinical development trial phases will be less than at the marketing registration phase. A risk-based approach based on process chemistry fundamentals is encouraged to prioritize analytical efforts on those impurities with the highest likelihood of being present in the drug substance or drug product. Analytical data may not be expected to support early clinical development when the likelihood of an impurity being present is low, but in a similar situation analytical data may be appropriate to support the control approach for the marketing application. It is also recognized that commercial formulation design occurs later in clinical development and therefore efforts associated with drug product degradation products will be limited in the earlier phases.

9. Documentation

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

9.1. Clinical Trial Applications

- It is expected that the number of structures assessed for mutagenicity, and the collection of analytical data will both increase throughout the clinical development period.

- For Phase 1 studies of 14 days or less a description of efforts to mitigate risks of mutagenic impurities focused on Class 1, and Class 2 impurities and those in the cohort of concern as outlined in Section 7 should be included. For Phase 1 clinical trials greater than 14 days and for Phase 2a clinical trials additionally Class 3 impurities that require analytical controls should be included.

- For Phase 2b and Phase 3 clinical development trials, a list of the impurities assessed by (Q)SAR should be included, and any Class 1, 2 or 3 actual and potential impurities should be described along with plans for control. The in silico (Q)SAR systems used to perform the assessments should be described. The results of bacterial mutagenicity tests of actual impurities should be reported.

- Chemistry arguments may be appropriate instead of analytical data for potential impurities that present a low likelihood of being present as described in Section 8.6.

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9.2. Common Technical Document (Marketing Application)

- For actual and potential process related impurities and degradation products where assessments according to this guideline are conducted, the mutagenic impurity classification and rationale for this classification should be provided:

    o This would include the results and description of *in silico* (Q)SAR systems used, and as appropriate, supporting information to arrive at the overall conclusion for Class 4 and 5 impurities.

    o When bacterial mutagenicity assays were performed on impurities, study reports should be provided for bacterial mutagenicity assays on impurities.

- Justification for the proposed specification and the approach to control should be provided (e.g., ICH Q11 example 5b, Ref. 12). For example, this information could include the acceptable intake, the location and sensitivity of relevant routine monitoring. For Option 3 and Option 4 control approaches, a summary of knowledge of the purge factor, and identification of factors providing control (e.g., process steps, solubility in wash solutions, etc.) is important.

NOTES

Note 1

The ICH M7 Guideline recommendations provide a state-of-the-art approach for assessing the potential of impurities to induce point mutations and ensure that such impurities are controlled to safe levels so that below or above the ICH Q3A/B qualification threshold no further qualification for mutagenic potential is required. This includes the initial use of (Q)SAR tools to predict bacterial mutagenicity. In cases where the amount of the impurity exceeds 1 mg daily dose for chronic administration, evaluation of genotoxic potential as recommended in ICH Q3A/B could be considered. In cases where the amount of the impurity is equal to or less than 1 mg, no further genotoxicity testing is required regardless of other qualification thresholds.

Note 2

To assess the mutagenic potential of impurities, a single bacterial mutagenicity assay can be carried out with a fully adequate protocol according to ICH S2(R1) and OECD 471 guidelines (Ref. 13 and 14). The assays are expected to be performed in compliance with Good Laboratory Practices (GLP) regulations; however, 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. For example, the test article may not be prepared or analyzed in compliance with GLP regulations. In some cases, the selection of bacterial tester strains may be limited to those proven to be sensitive to the identified alert. For impurities that are not feasible to isolate or synthesize or when compound quantity is limited, it may not be possible to achieve the highest test concentrations recommended for an ICH-compliant bacterial mutagenicity assay according to the current testing guidelines. In this case, bacterial mutagenicity testing could be carried out using a miniaturized assay format with proven high concordance to the ICH-compliant assay to enable testing at higher concentrations with justification.

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Note 3

Tests to Investigate the in vivo Relevance of in vitro Mutagens (Positive Bacterial Mutagenicity)

In vivo test	Factors to justify choice of test as fit-for-purpose
Transgenic mutation assays	• For any bacterial mutagenicity positive. Justify selection of assay tissue/organ
Pig-a assay (blood)	• For directly acting mutagens (bacterial mutagenicity positive without S9)*
Micronucleus test (blood or bone marrow)	• For directly acting mutagens (bacterial mutagenicity positive without S9) and compounds known to be clastogenic*

Rat liver Unscheduled DNA Synthesis (UDS) test	• In particular for bacterial mutagenicity positive with S9 only
	• Responsible liver metabolite known
	  o to be generated in test species used
	
	  o to induce bulky adducts

Comet assay	• Justification needed (chemical class specific mode of action to form alkaline labile sites or single-strand breaks as preceding DNA damage that can potentially lead to mutations • Justify selection of assay tissue/organ
Others	• With convincing justification

*For indirect acting mutagens (requiring metabolic activation), adequate exposure to metabolite(s) should be demonstrated.

Note 4

Example of linear extrapolation from the TD50

It is possible to calculate a compound-specific acceptable intake based on rodent carcinogenicity potency data such as TD50 values (doses giving a 50% tumor incidence equivalent to a cancer risk probability level of 1:2). Linear extrapolation to a probability of 1 in 100,000 (i.e., the accepted lifetime risk level used) is achieved by simply dividing the TD50 by 50,000. This procedure is similar to that employed for derivation of the TTC.
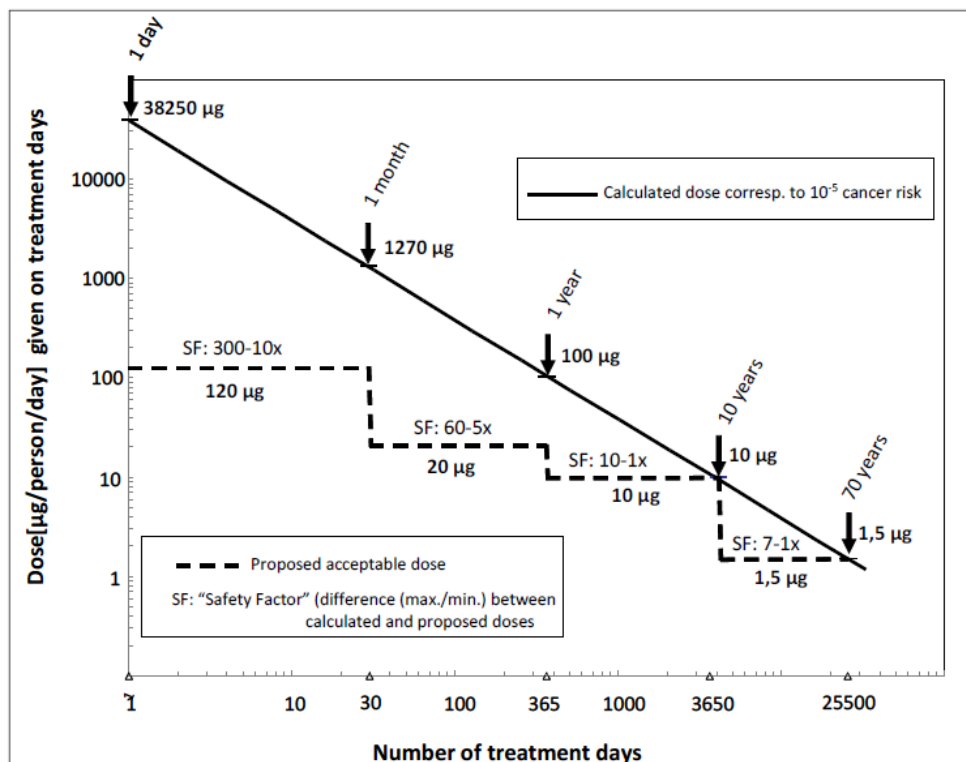
Calculation example: Ethylene oxide

TD50 values for ethylene oxide according to the Carcinogenic Potency Database are

21.3 mg/kg body weight/day (rat) and 63.7 mg/kg body weight/day (mouse). For the calculation of an acceptable intake, the lower (i.e., more conservative) value of the rat is used.

To derive a dose to cause tumors in 1 in 100,000 animals, divide by 50,000:

21.3 mg/kg ÷ 50,000 = 0.42 µg/kg

To derive a total human daily dose:

0.42 µg/kg/day x 50 kg body weight = 21.3 µg/person/day

Hence, a daily life-long intake of 21.3 µg ethylene oxide would correspond to a theoretical cancer risk of 10^{-5} and therefore be an acceptable intake when present as an impurity in a drug substance.

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Alternative methods and published regulatory limits for cancer risk assessment

As an alternative of using the most conservative TD_{50} value from rodent carcinogenicity studies irrespective of its relevance to humans, an in-depth toxicological expert assessment of the available carcinogenicity data can be done in order to initially identify the findings (species, organ, etc.) with highest relevance to human risk assessment as a basis for deriving a reference point for linear extrapolation. Also, in order to better take into account directly the shape of the dose-response curve, a benchmark dose such as a Benchmark Dose Lower Confidence Limit 10% (BMDL10, an estimate of the lowest dose which is 95% certain to cause no more than a 10% cancer incidence in rodents) may be used instead of TD_{50} values as a numerical index for carcinogenic potency. Linear extrapolation to a probability of 1 in 100,000 (i.e., the accepted lifetime risk level used) is then achieved by simply dividing the BMDL10 by 10,000.

Compound-specific acceptable intakes can also be derived from published recommended values from internationally recognized bodies such as World Health Organization (WHO, International Program on Chemical Safety [IPCS] Cancer Risk Assessment Programme) and others using the appropriate 10^{-5} lifetime risk level. In general, a regulatory limit that is applied should be based on the most current and scientifically supported data and/or methodology.

Note 5

A compound-specific calculation of acceptable intakes for mutagenic impurities may be applied for mutagenic impurities (without carcinogenicity data) which are structurally similar to a chemically-defined class of known carcinogen. For example, factors that are associated with the carcinogenic potency of monofunctional alkyl chlorides have been identified (Ref. 15) and can be used to modify the safe acceptable intake of monofunctional alkyl chlorides, a group of alkyl chlorides commonly used in drug synthesis. Compared to multifunctional alkyl chlorides the monofunctional compounds are much less potent carcinogens with TD_{50} values ranging from 36 to 1810 mg/kg/day (n=15; epichlorohydrin with two distinctly different functional groups is excluded). A TD_{50} value of 36 mg/kg/day can thus be used as a still very conservative class-specific potency reference point for calculation of acceptable intakes for monofunctional alkyl chlorides. This potency level is at least ten-fold lower than the TD_{50} of 1.25 mg/kg/day corresponding to the default lifetime TTC (1.5 µg/day) and therefore justifies lifetime and less-than-lifetime daily intakes for monofunctional alkyl chlorides ten times the default ones.

Note 6

Establishing less-than-lifetime acceptable intakes for mutagenic impurities in pharmaceuticals has precedent in the establishment of the staged TTC limits for clinical development (Ref. 16). The calculation of less-than-lifetime Acceptable Intakes (AI) is predicated on the principle of Haber's rule, a fundamental concept in toxicology where concentration (C) x time (T) = a constant (k). Therefore, the carcinogenic effect is based on both dose and duration of exposure.

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Figure 1: Illustration of calculated daily dose of a mutagenic impurity corresponding to a theoretical 1:100,000 cancer risk as a function of duration of treatment in comparison to the acceptable intake levels as recommended in Section 7.3.

The solid line in Figure 1 represents the linear relationship between the amount of daily intake of a mutagenic impurity corresponding to a 10^{-5} cancer risk and the number of treatment days. The calculation is based on the TTC level as applied in this guideline for life-long treatment i.e., 1.5 μg per person per day using the formula:

$$\text{Less-than-lifetime AI} = \frac{\underline{1.5 \text{ μg} \times (365 \text{ days} \times 70 \text{ years lifetime} = 25,550)}}{\text{Total number of treatment days}}$$

The calculated daily intake levels would thus be 1.5 μg for treatment duration of 70 years, 10 μg for 10 years, 100 μg for 1 year, 1270 μg for 1 month and approximately

38.3 mg as a single dose, all resulting in the same cumulative intake and therefore theoretically in the same cancer risk (1 in 100,000).

The dashed step-shaped curve represents the actual daily intake levels adjusted to less-than-lifetime exposure as recommended in Section 7 of this guideline for products in clinical development and marketed products. These proposed levels are in general significantly lower than the calculated values thus providing safety factors that increase with shorter treatment durations.

The proposed accepted daily intakes are also in compliance with a 10^{-6} cancer risk level if treatment durations are not longer than 6 months and are therefore applicable in early clinical trials with volunteers/patients where benefit has not yet been established. In this case the safety factors as shown in the upper graph would be reduced by a factor of 10.

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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 $\leq$ 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 ($\sim$ 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	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 Disease (COPD), cystic fibrosis, seasonal and perennial allergic rhinitis, HIV[3]	1.5

[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 years category.

[3] Changed in M7(R2) from 1-10 years to >10 years to lifetime because of clinical treatment advances. See Q&A.

Glossary

Acceptable intake:

In the context of this guideline, an intake level that poses negligible cancer risk, or for serious/life-threatening indications where risk and benefit are appropriately balanced.

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Acceptable limit:

Maximum acceptable concentration of an impurity in a drug substance or drug product derived from the acceptable intake and the daily dose of the drug.

Acceptance criterion:

Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures.

Control strategy:

A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

Cumulative intake:

The total intake of a substance that a person is exposed to over time.

Degradation Product:

A molecule resulting from a chemical change in the drug molecule brought about over time and/or by the action of light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system.

DNA-reactive:

The potential to induce direct DNA damage through chemical reaction with DNA.

Expert knowledge:

In the context of this guideline, expert knowledge can be defined as a review of pre-existing data and the use of any other relevant information to evaluate the accuracy of an *in silico* model prediction for mutagenicity.

Genotoxicity:

A broad term that refers to any deleterious change in the genetic material regardless of the mechanism by which the change is induced.

Impurity:

Any component of the drug substance or drug product that is not the drug substance or an excipient.

Mutagenic impurity:

An impurity that has been demonstrated to be mutagenic in an appropriate mutagenicity test model, e.g., bacterial mutagenicity assay.

Periodic verification testing:

Also known as periodic or skip testing in ICH Q6A.

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(Q)SAR and SAR:

In the context of this guideline, refers to the relationship between the molecular (sub) structure of a compound and its mutagenic activity using (Quantitative) Structure-Activity Relationships derived from experimental data.

Purge factor:

Purge reflects the ability of a process to reduce the level of an impurity, and the purge factor is defined as the level of an impurity at an upstream point in a process divided by the level of an impurity at a downstream point in a process. Purge factors may be measured or predicted.

Structural alert:

In the context of this guideline, a chemical grouping or molecular (sub) structure which is associated with mutagenicity.

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Appendices

Appendix 1: Scope Scenarios for Application of the ICH M7 Guideline

Scenario	Applies to Drug Substance	Applies to Drug Product	Comments
Registration of new drug substances and associated drug product	Yes	Yes	Primary intent of the M7 Guideline
Clinical trial applications for new drug substances and associated drug product	Yes	Yes	Primary intent of the M7 Guideline
Clinical trial applications for new drug substances for a anticancer drug per ICH S9	No	No	Out of scope of M7 Guideline
Clinical trial applications for new drug substances for an orphan drug	Yes	Yes	There may be exceptions on a case by case basis for higher impurity limits
Clinical trial application for a new drug product using an existing drug substance where there are no changes to the drug substance manufacturing process	No	Yes	Retrospective application of the M7 Guideline is not intended for marketed products unless there are changes made to the synthesis. Since no changes are made to the drug substance synthesis, the drug substance would not require reevaluation. Since the drug product is new, application of this guideline is expected.
A new formulation of an approved drug substance is filed	No	Yes	See Section 4.2

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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.	Yes	Yes	As there is no mutual recognition, an existing product in one member region filed for the first time in another member region would be considered a new product.
A new supplier or new site of the drug substance is registered. There are no changes to the manufacturing process used in this registered application.	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 changes have been made to a previously approved process/product. See Section 4.1.

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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	Yes	Yes	Since the patient population and acceptable cancer risk have changed, the previously approved impurity control strategy and limits will require reevaluation. See Section 4.3.
New combination product is filed that contains one new drug substance and an existing drug substance	Yes (new drug substance) No (existing drug substance)	Yes	M7 would apply to the new drug substance. For the existing drug substance, retrospective application of M7 to existing products is not intended. For the drug product, this would classify as a new drug product so the guideline would apply to any new or higher levels of degradation products.

Appendix 2: Case Examples to Illustrate Potential Control Approaches

Case 1: Example of an Option 3 Control Strategy

An intermediate X is formed two steps away from the drug substance and impurity A is routinely detected in intermediate X. The impurity A is a stable compound and carries over to the drug substance. A spike study of the impurity A at different concentration levels in intermediate X was performed at laboratory scale. As a result of these studies, impurity A was consistently removed to less than 30% of the TTC-based limit in the drug substance even when impurity A was present at 1% in intermediate X. Since this intermediate X is formed only two steps away from the drug substance and the impurity A level in the intermediate X is relatively high, the purging ability of the process has additionally been confirmed by determination of impurity A in the drug substance in multiple pilot-scale batches and results were below 30% of the TTC-based limit. Therefore, control of the impurity A in the intermediate X with an acceptance limit of 1.0% is justified and no test is warranted for this impurity in the drug substance specification.

Case 2: Example of an Option 3 Control Strategy: Based on Predicted Purge from a Spiking Study Using Standard Analytical Methods

A starting material Y is introduced in step 3 of a 5-step synthesis and an impurity B is routinely detected in the starting material Y at less than 0.1% using standard analytical methods. In order to determine if the 0.1% specification in the starting material is acceptable, a purge study was conducted at laboratory scale where impurity B was spiked into starting material Y with different concentration levels up to 10% and a purge factor of > 500-fold was determined across the final three processing steps. This purge factor applied to a 0.1% specification in starting material Y would result in a predicted level of impurity B in the drug substance of less than 2 ppm. As this is below the TTC-based limit of 50 ppm for this impurity in the drug substance, the 0.1% specification of impurity B in starting material Y is justified without the need for providing drug substance batch data on pilot scale or commercial scale batches.

Case 3: Example of an Option 2 and 4 Control Strategy: Control of Structurally Similar Mutagenic Impurities

The step 1 intermediate of a 5-step synthesis is a nitroaromatic compound that may contain low levels of impurity C, a positional isomer of the step 1 intermediate and also a nitroaromatic compound. The amount of impurity C in the step 1 intermediate has not been detected by ordinary analytical methods, but it may be present at lower levels. The step 1 intermediate is positive in the bacterial mutagenicity assay. The step 2 hydrogenation reaction results in a 99% conversion of the step 1 intermediate to the corresponding aromatic amine. This is confirmed via in-process testing. An assessment of purge of the remaining step 1 nitroaromatic intermediate was conducted and a high purge factor was predicted based on purge points in the subsequent step 3 and 4 processing steps. Purge across the step 5 processing step is not expected and a specification for the step 1 intermediate at the TTC- based limit was established at the step 4 intermediate (Option 2 control approach). The positional isomer impurity C would be expected to purge via the same purge points as the step 1 intermediate and therefore will always be much lower than the step 1 intermediate itself and therefore no testing is required and an Option 4 control strategy for impurity C can be supported without the need for any additional laboratory or pilot scale data.

Case 4: Example of an Option 4 Control Strategy: Highly Reactive Impurity

Thionyl chloride is a highly reactive compound that is mutagenic. This reagent is introduced in step 1 of a 5-step synthesis. At multiple points in the synthesis, significant amounts of water are used. Since thionyl chloride reacts instantaneously with water, there is no chance of any residual thionyl chloride to be present in the drug substance. An Option 4 control approach is suitable without the need for any laboratory or pilot scale data.
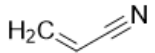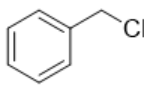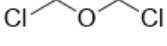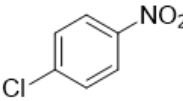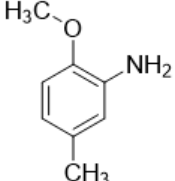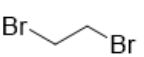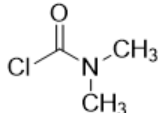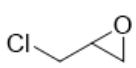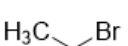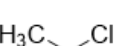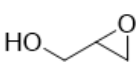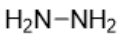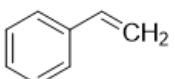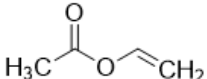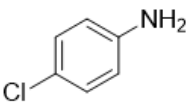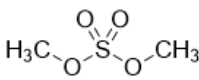
Implementation of Guideline:
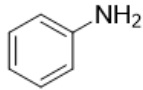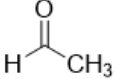
Implementation of M7 is encouraged after publication; however, because of the complexity of the guideline, application of M7 is not expected prior to 18 months after ICH publication.

The following exceptions to the 18-month timeline apply.

1. Ames tests should be conducted according to M7 upon ICH publication. However, Ames tests conducted prior to publication of M7 need not be repeated.

2. When development programs have started phase 2b/3 clinical trials prior to publication of M7 these programs can be completed up to and including marketing application submission and approval, with the following exceptions to M7.

   o No need for two QSAR assessments as outlined in Section 6.

   o No need to comply with the scope of product impurity assessment as outlined in Section 5.

   o No need to comply with the documentation recommendations as outlined in Section 9.

3. Given the similar challenges for development of a commercial manufacturing process, application of the aspects of M7 listed above to new marketing applications that do not include Phase 2b/3 clinical trials would not be expected until 36 months after ICH publication of M7.

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Appendix 3: List of Compounds in _ICH M7 Addendum_ Acceptable Intakes (AIs) or Permissible Daily Exposures (PDEs)

Compound	CAS#	Chemical Structure	AI or PDE (µg/day)	Comment
Linear extrapolation from TD50				
Acrylonitrile	107-13-1		6	TD50 linear extrapolation
Benzyl chloride	100-44-7		41	TD50 linear extrapolation
Bis(chloromethyl)ether	542-88-1		0.004	TD50 linear extrapolation
1-Chloro-4- nitrobenzene	100-00-5		117	TD50 linear extrapolation
_p_-Cresidine	120-71-8		45	TD50 linear extrapolation
1,2-Dibromoethane	106-93-4		2	TD50 linear extrapolation
Dimethylcarbamyl chloride	79-44-7		0.6 (inhalation)* 5 (all other routes)	TD50 linear extrapolation
Epichlorohydrin	106-89-8		3	TD50 linear extrapolation
Ethyl bromide	74-96-4		32	TD50 linear extrapolation
Ethyl chloride	75-00-3		1,810	TD50 linear extrapolation
Glycidol	556-52-5		4	TD50 linear extrapolation
Hydrazine	302-01-2		0.2 (inhalation)* 39 (all other routes)	TD50 linear extrapolation
Methyl Chloride	74-87-3		1,361	TD50 linear extrapolation
Styrene	100-42-5		154	TD50 linear extrapolation

Threshold-based PDE				
Aniline Aniline HCl	62-53-3 142-04-1		720	PDE based on threshold mode of action (hemosiderosis)

Endogenous and/or Environmental Exposure				
Acetaldehyde	75-07-0		2,000 (oral)* 185 (all other routes)	Oral PDE is based on average food intake; all other routes based on TD_{50} linear extrapolation from an inhalation study
Formaldehyde	50-00-0		8,000 or 215 ppb, whichever is lower (inhalation)* 10,000 (all other routes)	Inhalation route based on TD_{50} linear extrapolation or local irritation; all other routes based on average food intake
Hydrogen peroxide	7722-84-1	HO—OH	68,000 or 0.5%, whichever is lower	68 mg/day is 1% of estimated endogenous production
Vinyl acetate	108-05-4		2,000 (oral)* 758 (all other routes)	Oral PDE is based on average food intake for acetaldehyde; all other routes based on TD_{50} linear extrapolation from an inhalation study

Other Cases				
p-Chloroaniline p-Chloroaniline HCl	106-47-8 20265-96-7		34	AI based on liver tumors for which mutagenic mode of action cannot be ruled out
Dimethyl Sulfate	77-78-1		1.5	Carcinogenicity data available, but inadequate to derive AI. Default to TTC

* route specific limit

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