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

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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 (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 can be applied for 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 (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 new marketing applications and post approval submissions for marketed products, 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 degradants or increased acceptance criteria for existing degradants;
- Changes in indication or dosing regimen are made which significantly affect the acceptable cancer risk level.

The following types of drug substances are not covered in this guideline: biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation products, herbal products, and crude products of animal or plant origin. Exceptions would be when products such as biologicals and peptides are chemically synthesized or modified (e.g., addition of organic chemical linkers, semi-synthetic products). In such cases an assessment of potential mutagenicity is warranted for chemicals likely to exist as impurities/degradants in the drug product.

This guideline does not apply to drug substances and drug products intended for advanced cancer indications as defined in the scope of ICH S9 (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 and impurities could be controlled at acceptable levels for non-mutagenic impurities.

Excipients used in existing marketed products and flavoring agents are excluded from this guideline. 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 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 thresholded mechanisms (5-9) 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/effect and the need for controls. Structure-based assessments are useful for predicting bacterial mutagenicity outcomes based upon the established knowledge base. 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 will not pose a risk of carcinogenicity or other toxic effects (10-11). For application of a TTC in the assessment of acceptable limits of mutagenic impurities in drug substances and drug product, a value of 1.5 μg/day corresponding to a theoretical 10-5 excess lifetime risk of cancer, can be justified. The methods upon which the TTC is based are generally considered very conservative since they involve a simple linear extrapolation from the dose giving a 50% tumour incidence (TD50) to a 1 in 106 incidence, using TD50 data for the most sensitive species and most sensitive site of tumour induction (several "worst case" assumptions) (10). 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 (12-13). 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 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 marketed products when efficacy has been shown, 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 (14-15). 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 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. 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 (13). 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 these 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 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 impurity is considered qualified provided that exposure to the metabolite in appropriate nonclinical studies of the drug substance is higher than would be achieved from the impurity in the administered drug substance (ICH Q3A/Q3B).

4. Considerations for marketed products

While this guideline is not intended to be applied retrospectively (i.e., to products marketed prior to adoption of this guideline), some types of post-approval changes warrant a reassessment of safety relative to mutagenic impurities. This Section is intended to be applied to 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 (changes to the route of synthesis, reagents, solvents, process conditions etc.) should include an evaluation of the potential risk impact associated with mutagenic impurities. Specifically, changes should be evaluated to determine if the change results in any new mutagenic impurities or higher acceptance criteria for existing mutagenic impurities. Re-evaluation of impurities not impacted by the change is not required. 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 include a summary of the assessment and if appropriate an updated control strategy. Changes to site of manufacture would typically not require a reassessment of mutagenic impurity risk.

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 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 degradants or higher acceptance criteria for existing mutagenic degradants. If appropriate, the regulatory submission would include an updated control strategy. Re-evaluation of the drug substance associated with drug products is not required or expected provided there are no changes to the drug substance. Changes to site of manufacture would typically not require a reassessment of mutagenic impurity risk.

4.3. Changes to the clinical use of marketed products

Changes to the clinical use of marketed products that typically may require a re-evaluation 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 paediatrics typically would not require a re-evaluation, assuming no changes in daily dose or duration of treatment.

4.4. Alternative 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 (see 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 to marketing application holders. When the applicant becomes aware of this new relevant impurity hazard data, an evaluation should be conducted and if it is concluded by the applicant to affect the acceptable cancer risk/benefit, notification (Section 9) to regulatory authorities with a proposed contemporary control strategy would be warranted.

5. Drug substance and drug product impurity assessment

Actual and potential impurities that are likely to arise during the synthesis, work-up, 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. Firstly, actual impurities that have been identified should be considered for their mutagenic potential. In parallel, 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 degradants 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 arising from the synthesis of the drug substance could include starting materials, reagents and intermediates, identified impurities in starting materials and intermediates, and reasonably expected reaction by-products based on knowledge of the chemical reactions and conditions involved. 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, especially when there is a reasonable expectation that such impurities may be carried through the synthesis to the drug substance.

All impurities (actual and potential), where the structures are known, should be evaluated for mutagenic potential as described in Section 6.

5.2. Degradants

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 drug product degradation products 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 degradants in the drug substance and drug product are those that may be reasonably expected to form during long term storage conditions. Potential degradants include those that form above the ICHQ3A/B identification threshold during accelerated stability studies (e.g. 40oC/75% relative humidity for 6 months) and confirmatory photo-stability studies as described in ICH Q1B (16), but are yet to be confirmed in the drug substance or drug product 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 degradants 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 6.

5.3. Considerations for clinical development

For products in clinical development, the thresholds outlined in ICHQ3A/B do not apply and it is acknowledged that the thresholds for actual impurities and degradants will typically be higher than those outlined in ICHQ3A/B.

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 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 (according to Ref. 17 with modifications)

Class	Definition	Proposed action for control
1	Known mutagenic carcinogens	Control at or below compound-specific acceptable limit
2	Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive*, no rodent carcinogenicity data)	Control at or below acceptable limits (generic or adjusted TTC)
3	Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data	Control at or below acceptable limits (generic or adjusted TTC) or do bacterial mutagenicity assay; If non-mutagenic = Class 5 If mutagenic = Class 2
4	Alerting structure, same alert in drug substance which has been tested and is non-mutagenic	Treat as non-mutagenic impurity
5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity	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. 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 validation principles set forth by the OECD (18).

The outcome of any computer system-based analysis should be reviewed with the use of expert knowledge in order to provide additional supportive evidence on relevance of any positive or negative prediction and to elucidate underlying reasons in case of conflicting results.

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 concern, and no further testing is required (Class 5 in Table 1).

To follow up on a structural alert (Class 3 in Table 1), a bacterial mutagenicity assay can be applied. An appropriately conducted negative bacterial mutagenicity assay (Note 2) would overrule any structure-based concern, and no further genotoxicity assessments would be required (Note 1). These impurities (Class 5 in Table 1) should be considered as a non-mutagenic impurity. A positive bacterial mutagenicity result would warrant further hazard assessment and/or control measures (Class 2 in Table 1). Alternatively adequate control measures in the case of a positive structural alert alone could be applied in place of bacterial mutagenicity testing.

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

Further hazard assessment of an impurity with a positive bacterial mutagenicity result (Class 2 in Table 1) may be appropriate for instance, when levels of the impurity cannot be controlled at an appropriate acceptable limit. In order to understand the relevance of the bacterial mutagenicity assay result under *in vivo* conditions, it is recommended that the impurity is tested in an *in vivo* gene mutation assay. The selection of other *in vivo* genotoxicity assays should be scientifically justified based on knowledge of the mechanism of action of the impurity and its organ site of contact (Note 3). *In vivo* studies should be designed taking into consideration existing guidance as per ICH S2(R1) (19). Negative results in the appropriate *in vivo* assay may support setting impurity limits in excess of the acceptable limits.

7. Risk characterisation

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 into Classes 1, 2, and 3 (Class 3 only if presence of a structural alert is not followed up in a bacterial mutagenicity assay), the principles of risk characterization used to derive acceptable intakes are described in this section.

7.1. Generic 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 generic 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 bodies (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).

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 critical no-observed effect level (NOEL) and use of uncertainty factors (ICH Q3C(R5)) (20) when data are available (Note 6).

The acceptable intakes derived from compound-specific risk assessments can be adjusted for shorter term use in the same proportions as defined in the following sections (see Section 7.3.1 and 7.3.2).

7.3. Acceptable intakes in relation to less-than-lifetime (LTL) exposure

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 (21). 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. In the case of intermittent (non-daily) dosing, the acceptable intake will be capped by the total cumulative dose or the maximum acceptable intake (i.e. 120 µg/day), whichever is lower. Table 2 illustrates the acceptable intakes for LTL to lifetime exposures for clinical development and marketing.

Table 2: Acceptable intakes for an individual impurity

Duration of treatment	< 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 III 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 7).

An alternative approach to the strict use of an adjusted acceptable intake for any mutagenic impurity could be applied for Phase I clinical trials of up to 14 days. 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 I duration.

7.3.2. Marketed products

Standard risk assessments of known carcinogens operate under the assumption 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 or lifetime average daily dose. This assumption has been advocated by other regulatory agencies (22) and proposed elsewhere (21).

For marketed product treatments with cumulative intakes of less than 10 years (continuous or total of intermittent treatments), the acceptable intake can be adjusted to <10 µg/day. For marketed products with much shorter treatment duration indications, the acceptable intake values of Table 2 can be applied. The proposed intakes would all comply with the principle of not exceeding a 10-5 cancer risk level (Note 7).

7.4. Acceptable intakes for multiple mutagenic impurities

The TTC-based acceptable intakes should be applied to each individual impurity. When there are multiple mutagenic impurities specified on the drug substance specification, total mutagenic impurities should be limited as described in Table 3 for clinical development and marketed products:

Table 3: Acceptable intakes for total impurities

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

*For clinical development up to 3 years. Similar principles could be applied to marketed products with justification.

Only impurities that are specified on the drug substance specification contribute to the calculation for total. Degradants which form in the drug product would be controlled individually and a total limit would not be applied. The above approach 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 (23).

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.
- A disproportionally high number of members of some structural classes of mutagens, i.e. aflatoxin-like-, N-nitroso-, and azoxy structures, of which some may occur as impurities in pharmaceuticals, display extremely high carcinogenic potency. Acceptable intakes for these high-potency carcinogens would likely be significantly lower than the acceptable intakes defined in this guideline. While the principles of this guideline can be used, a case-by-case approach using e.g. carcinogenicity data from closely related structures, if available, usually needs to be developed to justify acceptable intakes for pharmaceutical development and marketed products.

The above risk approaches are applicable to all routes of administration and no corrections to acceptable intakes 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) (24). 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 mutagenic, 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, 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 mitigate mutagenic impurities in the drug product is consistent with risk management processes identified in ICH Q9 (25). 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.

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. It is considered possible to apply periodic (verification) testing per ICH Q6A (26).

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.

8.2. Discussion of control approaches

A control strategy that relies on process controls in lieu of analytical testing (Option 4) 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 or drug product above the acceptable limit is determined to be negligible. Elements of a scientific risk assessment/chemistry 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. This option 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.

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 necessary. 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) for 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 as low as reasonably practical, 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 drug substance or drug product fails an established specification, the drug producer should immediately revert to 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.

8.4. Control of degradants

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 oC/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 degradants 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 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 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 analyse the impact of the proposed changes is required. Additionally, improvements in analytical procedures may lead to identification of an existing impurity or a new 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 needed 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. The appropriate testing to analyse the impact of the proposed change could include, but is not limited to, an assessment of current and potential new impurities and an assessment of the test procedures' abilities to detect any new impurities. This testing should be performed at an appropriate point in the manufacturing process.

In some cases, the use of statistical process control and trending of process measurements that are important for an Option 3 or Option 4 approach can be useful for continued suitability and capability of processes to provide adequate control on the impurity.

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 needed to support early clinical development when the likelihood of an impurity being present is low, but in a similar situation analytical data may be needed 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 degradants 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 development 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 I clinical trials of 14 days or less, a summary of efforts to mitigate risks of mutagenic impurities focused on Class 1 and 2 impurities and those in the cohort of concern as outlined in Section 7 should be included.
- For other clinical development trials including Phase I studies of longer than 14 days, a list of the structures 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 stated.
- 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.

9.2. Common technical document (marketing application)

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

- 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.
- When bacterial mutagenicity assays were performed on impurities, all results and the study reports should be provided for any bacterial mutagenicity-negative impurities.

- Justification for the proposed specification and the approach to control should be provided (e.g., ICH Q11 example 5b) (27). 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.

10. 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 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 Q3 A/B could be considered.

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. The assays are expected to be performed in compliance with GLP regulations; however, it is noted that the test article may not be prepared or analysed 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. In some cases, the selection of bacterial tester strains may be limited to those proven to be sensitive to an alert. For degradants 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. Confidence in detection of mutagens requires testing concentrations at levels ≥250 μg/plate (28).

Note 3

Tests to investigate the *in vivo* relevance of *in vitro* mutagens (positive bacterial mutagenicity)

In vivo test	**Mechanistic data 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)*

In vivo test	**Mechanistic data to justify choice of test as fit-for-purpose**
Micronucleus test (blood or bone marrow)	• For directly acting mutagens (bacterial mutagenicity positive without S9) and compounds known to be clastogenic*
Rat liver UDS test	• In particular for bacterial mutagenicity positive with S9 only • Responsible liver metabolite known – to be generated in test species used – 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), justification needed for sufficient exposure to metabolite(s)

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% tumour 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 (29) 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 tumours 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.

Alternative methods and published regulatory limits for cancer risk assessment

As an alternative of using the most conservative TD50 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 TD50 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 WHO (IPCS Cancer Risk Assessment Programme) (30) 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 alkyl halides have been identified (31) and can be used to modify the safe acceptable intake of monofunctional alkyl halides, a group of alkyl halides commonly used in drug synthesis. Compared to multifunctional alkyl halides the monofunctional compounds are much less potent carcinogens with TD50 values ranging from 36 to 1810 mg/kg/day (n=15; epichlorohydrin with two distinctly different functional groups is excluded) (31). A TD50 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 halides. This potency level is at least ten fold lower than the TD50 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 halides ten times the default ones.

Note 6

Some published data give reliable experimental evidence for (practical) thresholds in the dose response for compounds that are positive for bacterial mutagenicity. This includes examples of thresholds in error-free repair capacity of the mutagenic DNA-ethylating agent ethyl methanesulfonate (EMS) (32) or similarly for methylating agents (33). Thresholds involving metabolic detoxification processes also appear to exist for 1, 3-butadiene (34). Further, a threshold for oxidative DNA damage associated with the build-up of hemosiderin has been shown for p-chloroaniline hydrochloride (35). Aside of mechanistic considerations supporting an experimentally observed threshold, it is important that a proper statistical analysis supports this assumption as well (36).

Note 7

Establishing less-than-lifetime acceptable intakes for mutagenic impurities in pharmaceuticals has precedent in the establishment of the staged TTC limits for clinical development (17). 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.

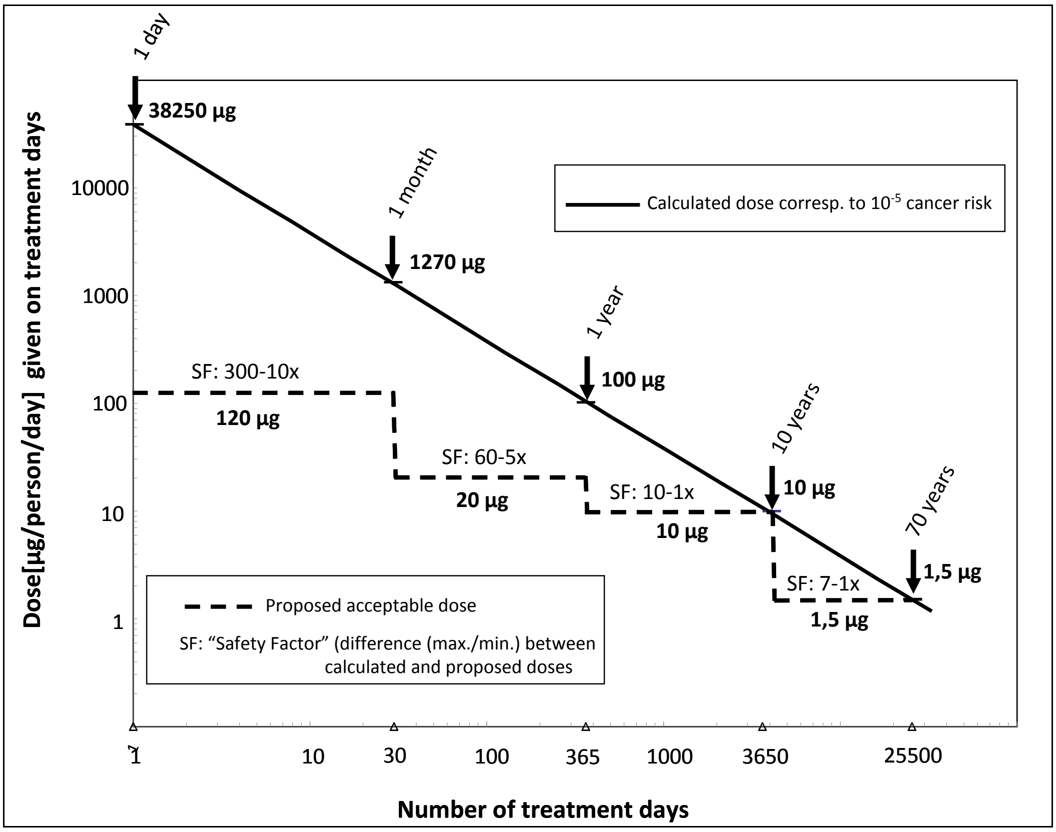

Figure 1: Illustration of calculated daily dose of a mutagenic impurity corresponding to a theoretical 1:100,000 cancer risk as a function of duration of treatment in comparison to the acceptable intake levels as recommended in Section 7.3.

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:

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

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 (SF) that increases 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.

*At 6 months the calculated dose at a 10-6 risk level would be 20 µg which is identical to the recommended accepted dose i.e. there is no extra safety factor; at longer duration the theoretical 10-6 risk level would be exceeded.

11. Glossary

Acceptable intake (AI): In the context of this guideline, an intake level that is without appreciable cancer risk.

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.

BMDL10: The lower 95% confidence interval of a Benchmark-dose representing a 10% response (e.g., tumor response upon lifetime exposure), i.e. the lower 95% confidence interval of a BMD10. BMD10 is the Benchmark-dose (BMD) associated with a 10% response adjusted for background.

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.

Degradant: Degradation product as defined in ICH Q3B.

DNA-reactive: Substances that have a potential to induce direct DNA damage through chemical reaction with DNA.

Expert knowledge: In the context of this guideline, expert knowledge can be generalized 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.

In-process control: Checks performed during production to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or drug substance conforms to its specifications.

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

NOEL: Abbreviation for no-observed-effect-dose (level): The highest dose of substance at which there are no biologically significant increases in frequency or severity of any effects in the exposed humans or animals.

Periodic (verification) testing: Also known as periodic or skip testing in ICH Q6A.

(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.

Statistical process control: Application of statistical methodology and procedures to analyse the inherent variability of a process.

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

TD50: The dose-rate in mg/kg body weight/day which, if administered chronically for the standard lifespan of the species, will halve the probability of remaining tumourless throughout that period.

Threshold: Categorically, a dose of a substance or exposure concentration below which a stated effect is not observed or expected to occur.

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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 an anti-cancer 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 re-evaluation. 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.
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 re-evaluation 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. Refer to section 4.1.
An existing product (approved after the issuance of ICH M7 with higher limits based on ICH S9) associated with an advanced	Yes	Yes	Since the patient population and acceptable cancer risk has changed, the previously approved impurity control strategy and limits will require re-

Scenario	Applies to Drug Substance	Applies to Drug Product	Comments
cancer indication is now registered for use in a non-life threatening indication.			evaluation. See section 4.3.
New combination product is filed that contains one new drug substance and an existing drug substance (no changes to the manufacturing process).	Yes (new drug substance) No (existing drug substance)	Yes	M7 guideline would apply to the new drug substance. For the existing drug substance, retrospective application of M7 guideline 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 degradants.

Appendix 2: Case examples to illustrate potential control approaches

Case 1: Example of an Option 3 control strategy

Impurity A: Intermediate X is introduced into the second to last step of the synthesis and impurity A is routinely detected in the intermediate material X. The impurity A is a stable compound and carries over to the drug substance. A spike study of the impurity A with different concentration levels was performed. As a result of these studies, it was determined that up to 1.0 % of the impurity A in the intermediate material X can be removed consistently to less than 30% of the TTC, 100 ppm in this case. This purge is consistent with the determined solubility of the impurity in the process solvents. This purge ability of the process has been confirmed by determination of any residue of impurity A in the drug substance in multiple pilot-scale batches and results ranged from 16-29 ppm. Therefore, control of the impurity A in the intermediate material X with an acceptance limit of 1.0 % is established. As the purge of impurity A is based on the solubility of the impurity in the process solvents and determined to be scale independent, submission of data on initial commercial batches would not be expected.

Case 2: Example of an Option 3 control strategy: Based on predicted purge from a spiking study using standard analytical methods

Impurity B: 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 testing in the drug substance 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 nitro aromatic 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 nitro aromatic 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 TTC levels 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.

Case 5: Option 1 control strategy: Application of Periodic Verification Testing

A mutagenic reagent is used in the last step of a drug substance synthesis. This reagent is a liquid at room temperature, is not used in excess, and is soluble in reaction and isolation solvents. A test and acceptance criteria for this reagent is contained in the drug substance specification due the fact that reagent is used in the final synthetic step. This impurity was tested for in the first 10 commercial batches and all test results were less than 5% of the acceptance criteria. In this situation, periodic verification testing could be accepted.