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

Step 3

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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

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

45 **3. General principles**

46 The focus of this guideline is on DNA reactive substances that have a potential to directly cause DNA
47 damage when present at low levels leading to mutations and therefore, potentially causing cancer.
48 This type of mutagenic carcinogen is usually detected in a bacterial reverse mutation (mutagenicity)
49 assay. Other types of genotoxicants that are non-mutagenic typically have thresholded mechanisms
50 (5-9) and usually do not pose carcinogenic risk in humans at the level ordinarily present as impurities.
51 Therefore to limit a possible human cancer risk associated with the exposure to potentially mutagenic
52 impurities, the bacterial mutagenicity assay is used to assess the mutagenic potential/effect and the
53 need for controls. Structure-based assessments are useful for predicting bacterial mutagenicity
54 outcomes based upon the established knowledge base. There are a variety of approaches to conduct
55 this evaluation including a review of the available literature, and/or computational toxicology
56 assessment.

57 A threshold of toxicological concern (TTC) concept was developed to define an acceptable intake for
58 any unstudied chemical that will not pose a risk of carcinogenicity or other toxic effects (10-11). For
59 application of a TTC in the assessment of acceptable limits of mutagenic impurities in drug substances
60 and drug product, a value of 1.5 µg/day corresponding to a theoretical 10⁻⁵ excess lifetime risk of
61 cancer, can be justified. The methods upon which the TTC is based are generally considered very
62 conservative since they involve a simple linear extrapolation from the dose giving a 50% tumour
63 incidence (TD50) to a 1 in 10⁶ incidence, using TD50 data for the most sensitive species and most
64 sensitive site of tumour induction (several "worst case" assumptions) (10). Some structural groups
65 were identified to be of such high potency that intakes even below the TTC would theoretically be
66 associated with a potential for a significant carcinogenic risk (12-13). This group of high potency
67 mutagenic carcinogens ("cohort of concern") comprises aflatoxin-like-, N-nitroso-, and azoxy
68 compounds.

69 During clinical development, it is expected that control strategies and approaches will be less
70 developed in earlier phases where overall development experience is limited. This guideline bases
71 acceptable intakes for mutagenic impurities on established risk assessment strategies. Acceptable risk
72 during the early development phase is set at a theoretically calculated level of approximately one
73 additional cancer per million. For later stages in development and marketed products when efficacy
74 has been shown, acceptable increased cancer risk is set at a theoretically calculated level of
75 approximately one in one hundred thousand. These risk levels represent a small theoretical increase in
76 risk when compared to human overall lifetime incidence of developing any type of cancer, which is
77 greater than 1 in 3 (14-15). It is noted that established cancer risk assessments are based on lifetime
78 exposures. Less-than-lifetime exposures both during development and marketing can have higher
79 acceptable intakes of impurities and still maintain comparable risk levels. The use of a numerical
80 cancer risk value (1 in 100,000) and its translation into risk-based doses (TTC) is a highly hypothetical
81 concept that should not be regarded as a realistic indication of the actual risk. The TTC concept
82 provides an estimate of safe exposures for any mutagenic compound. However, exceeding the TTC is
83 not necessarily associated with an increased cancer risk given the conservative assumptions employed
84 in the derivation of the TTC value. The most likely increase in cancer incidence is actually much less
85 than 1 in 100,000 (13). In addition, in cases where a mutagenic compound is a non-carcinogen in a
86 rodent bioassay, there would be no predicted increase in cancer risk. Based on these considerations,
87 any exposure to an impurity that is later identified as a mutagen is not necessarily associated with an

88 increased cancer risk for patients already exposed to the impurity. A risk assessment would determine
89 whether any further actions would be taken.

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

93 There may be cases when an impurity is also a metabolite of the drug substance. In such cases, the
94 impurity is considered qualified provided that exposure to the metabolite in appropriate nonclinical
95 studies of the drug substance is higher than would be achieved from the impurity in the administered
96 drug substance (ICH Q3A/Q3B).

97 **4. Considerations for marketed products**

98 While this guideline is not intended to be applied retrospectively (i.e., to products marketed prior to
99 adoption of this guideline), some types of post-approval changes warrant a reassessment of safety
100 relative to mutagenic impurities. This Section is intended to be applied to products marketed prior to,
101 or after, the adoption of this guideline. Section 8.5 (Lifecycle management) contains additional
102 recommendations for products marketed after adoption of this guideline.

103 ***4.1. Post approval changes to the drug substance chemistry, 104 manufacturing, and controls***

105 Post approval submissions involving the drug substance chemistry, manufacturing, and controls
106 (changes to the route of synthesis, reagents, solvents, process conditions etc.) should include an
107 evaluation of the potential risk impact associated with mutagenic impurities. Specifically, changes
108 should be evaluated to determine if the change results in any new mutagenic impurities or higher
109 acceptance criteria for existing mutagenic impurities. Re-evaluation of impurities not impacted by the
110 change is not required. For example, when only a portion of the manufacturing process is changed,
111 the assessment of risk from mutagenic impurities should be limited to whether any new mutagenic
112 impurities result from the change, whether any mutagenic impurities formed during the affected step
113 are increased, and whether any known mutagenic impurities from up-stream steps are increased.
114 Regulatory submissions associated with such changes should include a summary of the assessment
115 and if appropriate an updated control strategy. Changes to site of manufacture would typically not
116 require a reassessment of mutagenic impurity risk.

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

122 ***4.2. Post approval changes to the drug product chemistry, manufacturing, 123 and controls***

124 Post approval submissions involving the drug product (e.g., change in composition, manufacturing
125 process, dosage form) should include an evaluation of the potential risk associated with any new
126 mutagenic degradants or higher acceptance criteria for existing mutagenic degradants. If appropriate,
127 the regulatory submission would include an updated control strategy. Re-evaluation of the drug
128 substance associated with drug products is not required or expected provided there are no changes to

129 the drug substance. Changes to site of manufacture would typically not require a reassessment of
130 mutagenic impurity risk.

131 **4.3. Changes to the clinical use of marketed products**

132 Changes to the clinical use of marketed products that typically may require a re-evaluation of the
133 mutagenic impurity limits include a significant increase in clinical dose, an increase in duration of use
134 (in particular when a mutagenic impurity was controlled above the lifetime acceptable intake for a
135 previous indication that may no longer be appropriate for the longer treatment duration associated
136 with the new indication), or for a change in indication from a serious or life threatening condition where
137 higher acceptable intakes were justified (Section 7.5) to an indication for a less serious condition
138 where the existing impurity acceptable intakes may no longer be appropriate. Changes to the clinical
139 use of marketed products associated with new routes of administration or expansion into patient
140 populations that include pregnant women and/or paediatrics typically would not require a re-
141 evaluation, assuming no changes in daily dose or duration of treatment.

142 **4.4. Alternative considerations for marketed products**

143 Application of this guideline may be warranted to marketed products if there is specific cause for
144 concern. The existence of impurity structural alerts alone is considered insufficient to trigger follow-up
145 measures, unless it is a structure in the cohort of concern (see Section 3). However a specific cause
146 for concern would be new relevant impurity hazard data (classified as Class 1 or 2, Section 6)
147 generated after the overall control strategy and specifications for market authorization were
148 established. This new relevant impurity hazard data should be derived from high-quality scientific
149 studies consistent with relevant regulatory testing guidelines, with data records or reports readily
150 available to marketing application holders. When the applicant becomes aware of this new relevant
151 impurity hazard data, an evaluation should be conducted and if it is concluded by the applicant to
152 affect the acceptable cancer risk/benefit, notification (Section 9) to regulatory authorities with a
153 proposed contemporary control strategy would be warranted.

154 **5. Drug substance and drug product impurity assessment**

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

157 The impurity assessment is a two stage process. Firstly, actual impurities that have been identified
158 should be considered for their mutagenic potential. In parallel, an assessment of potential impurities
159 likely to be present in the final drug substance is carried out to determine if further evaluation of their
160 mutagenic potential is required. The steps as applied to synthetic impurities and degradants are
161 described in Sections 5.1 and 5.2, respectively.

162 **5.1. Synthetic impurities**

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

167 Potential impurities arising from the synthesis of the drug substance could include starting materials,
168 reagents and intermediates, identified impurities in starting materials and intermediates, and

169 reasonably expected reaction by-products based on knowledge of the chemical reactions and
170 conditions involved. Knowledge of the starting material synthesis, in particular the use of mutagenic
171 reagents is an important factor in understanding the potential impurities in the starting materials,
172 especially when there is a reasonable expectation that such impurities may be carried through the
173 synthesis to the drug substance.

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

176 **5.2. Degradants**

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

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

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

193 Actual and potential degradants likely to be present in the final drug substance or drug product and
194 where the structure is known should be evaluated for mutagenic potential as described in Section 6.

195 **5.3. Considerations for clinical development**

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

199 **6. Hazard assessment elements**

200 Hazard assessment involves an initial analysis of actual and potential impurities by conducting
201 database and literature searches for carcinogenicity and bacterial mutagenicity data in order to classify
202 them as Class 1, 2, or 5 according to Table 1. If data for such a classification are not available, an
203 assessment of structure-activity relationships (SAR) that focuses on bacterial mutagenicity predictions
204 should be performed. This could lead to a classification into Class 3, 4, or 5.

205

206

207

208 Table 1: Impurities Classification with Respect to Mutagenic and Carcinogenic Potential and Resulting
 209 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 |

210 *Or other relevant positive mutagenicity data indicative of DNA-reactivity related induction of gene mutations (e.g. positive findings
 211 in *in vivo* gene mutation studies)
 212

213 A computational toxicology assessment should be performed using (Q)SAR methodologies that predict
 214 the outcome of a bacterial mutagenicity assay. Two (Q)SAR prediction methodologies that
 215 complement each other should be applied. One methodology should be expert rule-based and the
 216 second methodology should be statistical-based. (Q)SAR models utilizing these prediction
 217 methodologies should follow the validation principles set forth by the OECD (18).

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

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

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

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

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

244 **7. Risk characterisation**

245 As a result of hazard assessment described in Section 6, each impurity will be assigned to one of the
246 five classes in Table 1. For impurities belonging into Classes 1, 2, and 3 (Class 3 only if presence of a
247 structural alert is not followed up in a bacterial mutagenicity assay), the principles of risk
248 characterization used to derive acceptable intakes are described in this section.

249 **7.1. Generic TTC-based acceptable intakes**

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

256 **7.2. Acceptable intakes based on compound-specific risk assessments**

257 **7.2.1. Mutagenic impurities with positive carcinogenicity data (class 1 in** 258 **table 1)**

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

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

268 **7.2.2. Mutagenic impurities with evidence for a practical threshold**

269 The existence of mechanisms leading to a dose response that is non-linear or has a practical threshold
270 is increasingly recognized, not only for compounds that interact with non-DNA targets but also for
271 DNA-reactive compounds, whose effects may be modulated by, for example, rapid detoxification before
272 coming into contact with DNA, or by effective repair of induced damage. The regulatory approach to
273 such compounds can be based on the identification of a critical no-observed effect level (NOEL) and
274 use of uncertainty factors (ICH Q3C(R5)) (20) when data are available (Note 6).

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

277 **7.3. Acceptable intakes in relation to less-than-lifetime (LTL) exposure**

278 The TTC-based acceptable intake of 1.5 µg/day is considered to be protective for a lifetime of daily
279 exposure. To address LTL exposures to mutagenic impurities in pharmaceuticals, an approach is
280 applied in which the acceptable cumulative lifetime dose (1.5 µg/day x 25,550 days = 38.3 mg) is
281 uniformly distributed over the total number of exposure days during LTL exposure (21). This would
282 allow higher daily intake of mutagenic impurities than would be the case for lifetime exposure and still
283 maintain comparable risk levels for daily and non-daily treatment regimens. In the case of
284 intermittent (non-daily) dosing, the acceptable intake will be capped by the total cumulative dose or
285 the maximum acceptable intake (i.e. 120 µg/day), whichever is lower. Table 2 illustrates the
286 acceptable intakes for LTL to lifetime exposures for clinical development and marketing.

287 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 |

288 **7.3.1. Clinical development**

289 Using this LTL concept, acceptable intakes of mutagenic impurities are recommended for limited
290 treatment periods during clinical development of up to 1 month, 1 to 12 months and more than one
291 year up to completion of Phase III clinical trials (Table 2). These adjusted acceptable intake values
292 maintain a 10⁻⁶ risk level in early clinical development when benefit has not yet been established and
293 a 10⁻⁵ risk level for later stages in development (Note 7).

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

301 **7.3.2. Marketed products**

302 Standard risk assessments of known carcinogens operate under the assumption that cancer risk
303 increases as a function of cumulative dose. Thus, cancer risk of a continuous low dose over a lifetime
304 would be equivalent to the cancer risk associated with an identical cumulative exposure averaged over
305 a shorter duration or lifetime average daily dose. This assumption has been advocated by other
306 regulatory agencies (22) and proposed elsewhere (21).

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

312 **7.4. Acceptable intakes for multiple mutagenic impurities**

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

316 Table 3: Acceptable intakes for total impurities

| Duration of treatment | < 1 month | >1 - 12 months | >1 - 10 years | >10 years to lifetime |
|-------------------------------------------|-----------|----------------|---------------|-----------------------|
| Daily intake [$\mu\text{g}/\text{day}$] | 120 | 60 | 10 (30*) | 5 |

317 *For clinical development up to 3 years. Similar principles could be applied to marketed products with justification.
318

319 Only impurities that are specified on the drug substance specification contribute to the calculation for
320 total. Degradants which form in the drug product would be controlled individually and a total limit
321 would not be applied. The above approach is supported by a detailed analysis of the effect of
322 combining multiple impurities that are in similar or different chemical classes and by the conservative
323 assumptions incorporated into the TTC, and the low likelihood of synergistic carcinogenic effects at
324 very low mutagenic impurity levels (23).

325 **7.5. Exceptions and flexibility in approaches**

- 326 • Higher acceptable intakes may be justified when human exposure to the impurity will be much
327 greater from other sources e.g., food, or endogenous metabolism (e.g., formaldehyde).
- 328 • Case-by-case exceptions to the use of the appropriate acceptable intake can be justified in cases of
329 severe disease, reduced life expectancy, late onset but chronic disease, or with limited therapeutic
330 alternatives.
- 331 • A disproportionately high number of members of some structural classes of mutagens, i.e. aflatoxin-
332 like-, N-nitroso-, and azoxy structures, of which some may occur as impurities in pharmaceuticals,
333 display extremely high carcinogenic potency. Acceptable intakes for these high-potency
334 carcinogens would likely be significantly lower than the acceptable intakes defined in this guideline.
335 While the principles of this guideline can be used, a case-by-case approach using e.g.
336 carcinogenicity data from closely related structures, if available, usually needs to be developed to
337 justify acceptable intakes for pharmaceutical development and marketed products.

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

343 **8. Control**

344 A control strategy is a planned set of controls, derived from current product and process understanding
345 that assures process performance and product quality (ICH Q10) (24). A control strategy can include,
346 but is not limited to, the following:

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

- 349 • Facility and equipment operating conditions
- 350 • Controls implicit in the design of the manufacturing process
- 351 • In-process controls (including in-process tests and process parameters)
- 352 • Controls on drug substance and drug product (e.g., release testing)

353 When an impurity has been characterized as mutagenic, it is important to develop a control strategy
354 that assures that the level of this impurity in the drug substance and drug product is below the
355 acceptable limit. A thorough knowledge of the chemistry associated with the drug substance
356 manufacturing process, the drug product manufacturing process, along with an understanding of the
357 overall stability of the drug substance and drug product is fundamental to developing the appropriate
358 controls. Developing a strategy to mitigate mutagenic impurities in the drug product is consistent with
359 risk management processes identified in ICH Q9 (25). A control strategy that is based on product and
360 process understanding and utilisation of risk management principles will lead to a combination of
361 process design and control and appropriate analytical testing, which can also provide an opportunity to
362 shift controls upstream and minimize the need for end-product testing.

363 **8.1. Control of process related impurities**

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

365 **Option 1**

366 Include a test for the impurity in the drug substance specification with an acceptance criterion at or
367 below the acceptable limit using an appropriate analytical procedure. It is considered possible to apply
368 periodic (verification) testing per ICH Q6A (26).

369 **Option 2**

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

373 **Option 3**

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

379 **Option 4**

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

383 **8.2. Discussion of control approaches**

384 A control strategy that relies on process controls in lieu of analytical testing (Option 4) can be
385 appropriate if the process chemistry and process parameters that impact levels of mutagenic impurities
386 are understood and the risk of an impurity residing in the final drug substance or drug product above
387 the acceptable limit is determined to be negligible. Elements of a scientific risk assessment/chemistry

388 rationale should include an assessment of various factors that influence the fate and purge of an
389 impurity including chemical reactivity, solubility, volatility, ionizability and any physical process steps
390 designed to remove impurities. This option is especially useful for those impurities that are inherently
391 unstable (e.g. thionyl chloride that reacts rapidly and completely with water) or for those impurities
392 that are introduced early in the synthesis and are effectively purged.

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

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

410 The application of 'as low as reasonably practicable' (ALARP) is not necessary if the level of the
411 mutagenic impurity is below acceptable limits. Similarly, it is not necessary to demonstrate that
412 alternate routes of synthesis have been explored.

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

416 **8.3. Considerations for periodic testing**

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

431 **8.4. Control of degradants**

432 For a potential degradant that has been characterized as mutagenic, it is important to understand if
433 the degradation pathway is relevant to the drug substance and drug product manufacturing processes
434 and/or their proposed packaging and storage conditions. A well-designed accelerated stability study
435 (e.g., 40 oC/75% relative humidity, 6 months) in the proposed packaging, with appropriate analytical
436 procedures is recommended to determine the relevance of the potential degradation product.
437 Alternatively, well designed kinetically equivalent shorter term stability studies at higher temperatures
438 in the proposed commercial package may be used to determine the relevance of the degradation
439 pathway prior to initiating longer term stability studies. This type of study would be especially useful
440 to understand the relevance of those potential degradants that are based on knowledge of potential
441 degradation pathways but not yet observed in the product.

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

450 If it is anticipated that formulation development and packaging design options are unable to control
451 mutagenic degradant levels to less than the acceptable limit and levels are as low as reasonably
452 practicable, a higher limit can be justified based on a risk/benefit analysis.

453 **8.5. Lifecycle management**

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

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

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

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

471 Throughout the lifecycle of the product, it will be important to reassess if testing is needed when
472 intended or unintended changes occur in the process. This applies when there is no routine monitoring
473 at the acceptable limit (Option 3 or Option 4 control approaches), or when applying periodic rather
474 than batch-by-batch testing. The appropriate testing to analyse the impact of the proposed change

475 could include, but is not limited to, an assessment of current and potential new impurities and an
476 assessment of the test procedures' abilities to detect any new impurities. This testing should be
477 performed at an appropriate point in the manufacturing process.

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

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

484 **8.6. Considerations for clinical development**

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

495 **9. Documentation**

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

497 **9.1. Clinical development trial applications**

- 498 • It is expected that the number of structures assessed for mutagenicity, and the collection of
499 analytical data will both increase throughout the clinical development period.
- 500 • For Phase I clinical trials of 14 days or less, a summary of efforts to mitigate risks of mutagenic
501 impurities focused on Class 1 and 2 impurities and those in the cohort of concern as outlined in
502 Section 7 should be included.
- 503 • For other clinical development trials including Phase I studies of longer than 14 days, a list of the
504 structures assessed by (Q)SAR should be included, and any Class 1, 2 or 3 actual and potential
505 impurities should be described along with plans for control. The in silico (Q)SAR systems used to
506 perform the assessments should be stated.
- 507 • Chemistry arguments may be appropriate instead of analytical data for potential impurities that
508 present a low likelihood of being present as described in Section 8.6.

509 **9.2. Common technical document (marketing application)**

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

- 513 – This would include the results and description of *in silico* (Q)SAR systems used, and as
 514 appropriate, supporting information to arrive at the overall conclusion for Class 4 and 5
 515 impurities.
- 516 – When bacterial mutagenicity assays were performed on impurities, all results and the study
 517 reports should be provided for any bacterial mutagenicity-negative impurities.
- 518 • Justification for the proposed specification and the approach to control should be provided (e.g.,
 519 ICH Q11 example 5b) (27). For example, this information could include the acceptable intake, the
 520 location and sensitivity of relevant routine monitoring. For Option 3 and Option 4 control
 521 approaches,, a summary of knowledge of the purge factor, and identification of factors providing
 522 control (e.g., process steps, solubility in wash solutions, etc.) is important.

523 10. Notes

524 Note 1

525 The ICH M7 guideline recommendations provide a state-of-the-art approach for assessing the potential
 526 of impurities to induce point mutations and ensure that such impurities are controlled to safe levels so
 527 that below or above the qualification threshold no further qualification for mutagenic potential is
 528 required. This includes the initial use of (Q)SAR tools to predict bacterial mutagenicity. In cases
 529 where the amount of the impurity exceeds 1 mg daily dose for chronic administration, evaluation of
 530 genotoxic potential as recommended in ICH Q3 A/B could be considered.

531 Note 2

532 To assess the mutagenic potential of impurities, a single bacterial mutagenicity assay can be carried
 533 out with a fully adequate protocol according to ICH S2(R1) and OECD 471 guidelines. The assays are
 534 expected to be performed in compliance with GLP regulations; however, it is noted that the test article
 535 may not be prepared or analysed in compliance with GLP regulations. Lack of full GLP compliance does
 536 not necessarily mean that the data cannot be used to support clinical trials and marketing
 537 authorizations. Such deviations should be described in the study report. In some cases, the selection
 538 of bacterial tester strains may be limited to those proven to be sensitive to an alert. For degradants
 539 that are not feasible to isolate or synthesize or when compound quantity is limited, it may not be
 540 possible to achieve the highest test concentrations recommended for an ICH-compliant bacterial
 541 mutagenicity assay according to the current testing guidelines. In this case, bacterial mutagenicity
 542 testing could be carried out using a miniaturized assay format with proven high concordance to the
 543 ICH-compliant assay to enable testing at higher concentrations with justification. Confidence in
 544 detection of mutagens requires testing concentrations at levels $\geq 250 \mu\text{g}/\text{plate}$ (28).

545 Note 3

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

| <i>In vivo</i> test | Mechanistic data to justify choice of test as fit-for-purpose |
|----------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| Transgenic mutation assays | <ul style="list-style-type: none"> For any bacterial mutagenicity positive. Justify selection of assay tissue/organ |
| Pig-a assay (blood) | <ul style="list-style-type: none"> For directly acting mutagens (bacterial mutagenicity positive without S9) * |

| <i>In vivo</i> test | Mechanistic data to justify choice of test as fit-for-purpose |
|---------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Micronucleus test (blood or bone marrow) | <ul style="list-style-type: none"> For directly acting mutagens (bacterial mutagenicity positive without S9) and compounds known to be clastogenic* |
| Rat liver UDS test | <ul style="list-style-type: none"> In particular for bacterial mutagenicity positive with S9 only Responsible liver metabolite known <ul style="list-style-type: none"> to be generated in test species used to induce bulky adducts |
| Comet assay | <ul style="list-style-type: none"> 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 | <ul style="list-style-type: none"> With convincing justification |

*For indirect acting mutagens (requiring metabolic activation), justification needed for sufficient exposure to metabolite(s)

547
548

549 **Note 4**

550 *Example of linear extrapolation from the TD50*

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

556 *Calculation example: Ethylene oxide*

557 TD50 values for ethylene oxide according to the Carcinogenic Potency Database (29) are 21.3 mg/kg
558 body weight/day (rat) and 63.7 mg/kg body weight/day (mouse). For the calculation of an acceptable
559 intake, the lower (i.e., more conservative) value of the rat is used.

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

561 $21.3 \text{ mg/kg} \div 50,000 = 0.42 \text{ } \mu\text{g/kg}$

562 To derive a total human daily dose:

563 $0.42 \text{ } \mu\text{g/kg/day} \times 50 \text{ kg body weight} = 21.3 \text{ } \mu\text{g/person/day}$

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

566 *Alternative methods and published regulatory limits for cancer risk assessment*

567 As an alternative of using the most conservative TD50 value from rodent carcinogenicity studies
568 irrespective of its relevance to humans, an in-depth toxicological expert assessment of the available
569 carcinogenicity data can be done in order to initially identify the findings (species, organ etc) with
570 highest relevance to human risk assessment as a basis for deriving a reference point for linear
571 extrapolation. Also, in order to better take into account directly the shape of the dose-response curve,

572 a benchmark dose such as a benchmark dose lower confidence limit 10% (BMDL10, an estimate of the
573 lowest dose which is 95% certain to cause no more than a 10% cancer incidence in rodents) may be
574 used instead of TD50 values as a numerical index for carcinogenic potency. Linear extrapolation to a
575 probability of 1 in 100,000 (i.e., the accepted lifetime risk level used) is then achieved by simply
576 dividing the BMDL10 by 10,000.

577 Compound-specific acceptable intakes can also be derived from published recommended values from
578 internationally recognized bodies such as WHO (IPCS Cancer Risk Assessment Programme) (30) and
579 others using the appropriate 10-5 lifetime risk level. In general, a regulatory limit that is applied
580 should be based on the most current and scientifically supported data and/or methodology.

581 **Note 5**

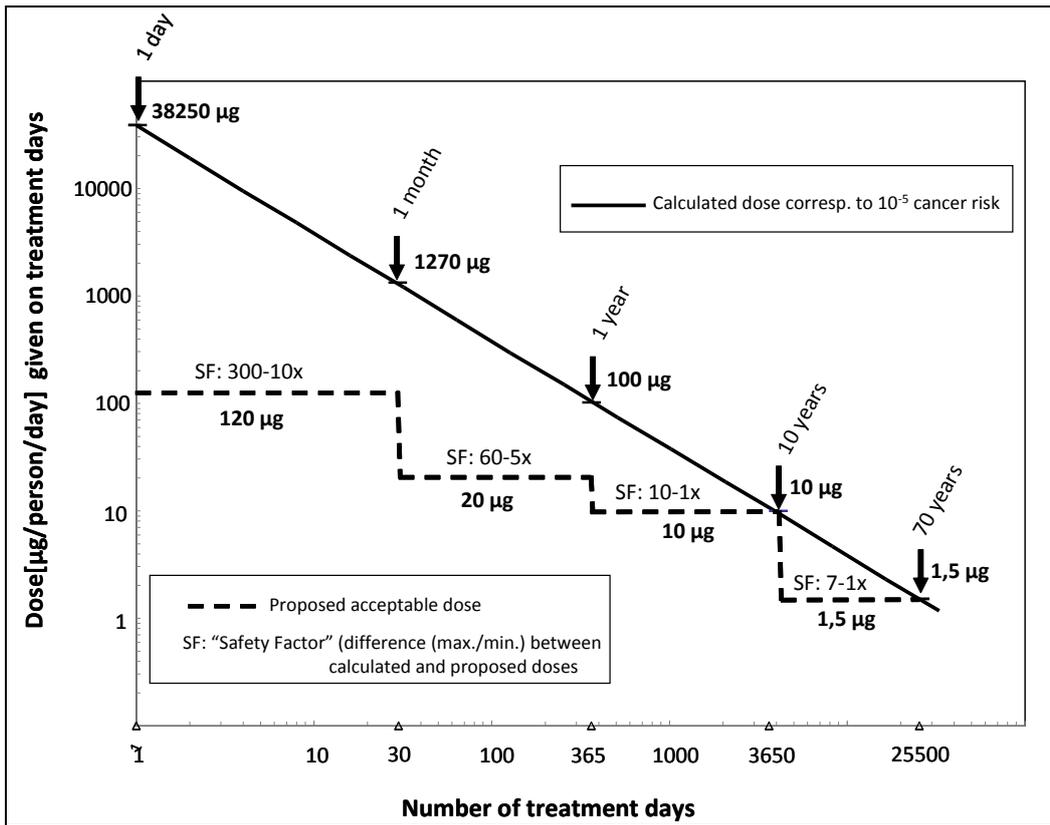
582 A compound-specific calculation of acceptable intakes for mutagenic impurities may be applied for
583 mutagenic impurities (without carcinogenicity data) which are structurally similar to a chemically-
584 defined class of known carcinogen. For example, factors that are associated with the carcinogenic
585 potency of alkyl halides have been identified (31) and can be used to modify the safe acceptable intake
586 of monofunctional alkyl halides, a group of alkyl halides commonly used in drug synthesis. Compared
587 to multifunctional alkyl halides the monofunctional compounds are much less potent carcinogens with
588 TD50 values ranging from 36 to 1810 mg/kg/day (n=15; epichlorohydrin with two distinctly different
589 functional groups is excluded) (31). A TD50 value of 36 mg/kg/day can thus be used as a still very
590 conservative class-specific potency reference point for calculation of acceptable intakes for
591 monofunctional alkyl halides. This potency level is at least ten fold lower than the TD50 of 1.25
592 mg/kg/day corresponding to the default lifetime TTC (1.5 µg/day) and therefore justifies lifetime and
593 less-than-lifetime daily intakes for monofunctional alkyl halides ten times the default ones.

594 **Note 6**

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

603 **Note 7**

604 Establishing less-than-lifetime acceptable intakes for mutagenic impurities in pharmaceuticals has
605 precedent in the establishment of the staged TTC limits for clinical development (17). The calculation
606 of less-than-lifetime acceptable intakes (AI) is predicated on the principle of Haber's rule, a
607 fundamental concept in toxicology where concentration (C) x time (T) = a constant (k). Therefore, the
608 carcinogenic effect is based on both dose and duration of exposure.



609

610 Figure 1: Illustration of calculated daily dose of a mutagenic impurity corresponding to a theoretical
 611 1:100,000 cancer risk as a function of duration of treatment in comparison to the acceptable intake
 612 levels as recommended in Section 7.3.

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

617
$$\text{Less-than-lifetime AI} = \frac{1.5 \mu\text{g} \times (365 \text{ days} \times 70 \text{ years lifetime} = 25,550)}{\text{Total number of treatment days}}$$

618

619 The calculated daily intake levels would thus be 1.5 µg for treatment duration of 70 years, 10 µg for 10
 620 years, 100 µg for 1 year, 1270 µg for 1 month and approximately 38.3 mg as a single dose, all
 621 resulting in the same cumulative intake and therefore theoretically in the same cancer risk (1 in
 622 100,000).

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

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

631 *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.
 632 there is no extra safety factor; at longer duration the theoretical 10⁻⁶ risk level would be exceeded.

633 11. Glossary

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

636 **Acceptable limit:** Maximum acceptable concentration of an impurity in a drug substance or drug
637 product derived from the acceptable intake and the daily dose of the drug.

638 **Acceptance criterion:** Numerical limits, ranges, or other suitable measures for acceptance of the
639 results of analytical procedures.

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

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

648 **Cumulative intake:** The total intake of a substance that a person is exposed to over time.

649 **Degradant:** Degradation product as defined in ICH Q3B.

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

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

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

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

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

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

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

665 **(Q)SAR and SAR:** In the context of this guideline, refers to the relationship between the molecular
666 (sub) structure of a compound and its mutagenic activity using (quantitative) structure-activity
667 relationships derived from experimental data.

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

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

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

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

677 **Threshold:** Categorically, a dose of a substance or exposure concentration below which a stated
678 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. |

777 **Appendix 2: Case examples to illustrate potential control**
778 **approaches**

779 **Case 1: Example of an Option 3 control strategy**

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

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

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

804 **Case 3: Example of an Option 2 and 4 control strategy: Control of structurally similar**
805 **mutagenic impurities**

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

820 **Case 4: Example of an Option 4 control strategy: Highly reactive impurity**

821 Thionyl chloride is a highly reactive compound that is mutagenic. This reagent is introduced in step 1
822 of a 5 step synthesis. At multiple points in the synthesis, significant amounts of water are used. Since
823 thionyl chloride reacts instantaneously with water, there is no chance of any residual thionyl chloride to
824 be present in the drug substance. An option 4 control approach is suitable without the need for any
825 laboratory or pilot scale data.

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

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