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4 Guideline on assessment and control of DNA reactive
5 (mutagenic) impurities in veterinary medicinal products
6 Draft

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Draft guideline on assessment and control of DNA reactive (mutagenic) impurities in veterinary medicinal products

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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 veterinary medicinal products (VMPs). While VICH GL10: Impurities in New Veterinary Drug Substances and VICH GL11: Impurities in New veterinary medicinal products provide guidance for qualification and control for the majority of the impurities, limited guidance is provided for those impurities that are DNA reactive. The purpose of this guideline is to provide a practical framework that is applicable to the identification, categorization, qualification, and control of these mutagenic impurities to limit potential carcinogenic risk. This guideline is intended to complement VICH GL10 and VICH GL11 (Note 1).

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 remain or are reasonably expected to remain in final drug substance or VMP.

The overall structure and approach of this guideline is based on that of the ICH guideline (M7, Ref 6) on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk. The ICH guideline was used as a template, with amendments introduced in order to cover the particularities of veterinary medicinal products.

2. Scope of guideline

This document is intended to provide guidance for new drug substances and new veterinary medicinal products. This includes new VMPs with drug substance(s) that have previously been present in authorised VMPs, but only in cases where:

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

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

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

This guideline applies to VMPs produced from chemically synthesized drug substances. It is not intended to apply to excipients used in existing authorised veterinary medicinal products or to the following types of drug substances and drug products: biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation products, herbal products, and crude products of animal or plant origin. However 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 veterinary medicinal product and are chemically synthesized.

The guideline aims to describe a framework for setting acceptable limits for genotoxic impurities with, in some cases, different considerations for companion and/or food-producing animals. It focuses particularly on risk (management) for the target animal, which is expected to receive a health benefit from exposure to the medicine. If the product is considered safe for a food-producing target animal then it can generally be assumed to also be safe for the consumer who could, theoretically, be exposed to DNA reactive impurities as a result of ingesting animal derived food commodities. It can be expected

88 that impurities are sufficiently diluted in the target animal and that a separate evaluation of the
89 consumer exposure to genotoxic impurities is therefore not routinely needed.

90 DNA reactive impurities should also be considered as part of the user risk assessment (URA) with
91 potential exposure being compared to the threshold of toxicological concern (TTC).

3. Legal Basis

93 Directive 2009/9/EC specifies that, in relation to the drug substance, information on the levels, nature
94 and safety of predictable impurities shall be provided. In relation to the finished product the directive
95 specifies that maximum levels of individual and total degradation products should be specified. The
96 guidelines named below address these requirements more specifically and this document should be
97 read in conjunction with these.

98 VICH GL10: Guideline on impurities in new veterinary drug substances (EMEA/CVMP/VICH/837/99-
99 Rev.1)

100 VICH GL11: Guideline on impurities in new veterinary medicinal products (EMEA/CVMP/VICH/838/99-
101 Rev.1)

102 VICH GL18(R): Impurities: Residual solvents in new veterinary medicinal products, actives substances
103 and excipients (Revision) (EMA/CVMP/VICH/502/99-Rev.1)

104 In addition, the guidance documents mentioned below provide useful background in relation to the
105 evaluation of genotoxic drug substances and impurities.

106 VICH GL23: Studies to evaluate the safety of residues of veterinary drugs in human food: genotoxicity
107 testing (EMA/CVMP/VICH/526/2000)

4. General principles

109 The focus of this guideline is on DNA reactive substances that have a potential to directly cause DNA
110 damage when present at low levels leading to mutations and therefore, potentially causing cancer.
111 This type of mutagenic carcinogen is usually detected in a bacterial reverse mutation (mutagenicity)
112 assay. Other types of genotoxicants that are non-mutagenic typically have threshold mechanisms and
113 usually do not pose carcinogenic risk in humans at the level ordinarily present as impurities. Therefore
114 to limit a possible cancer risk associated with the exposure to potentially mutagenic impurities, the
115 bacterial mutagenicity assay is used to assess the mutagenic potential and the need for controls.
116 Structure-based assessments are useful for predicting bacterial mutagenicity outcomes based upon the
117 established knowledge. There are a variety of approaches to conduct this evaluation including a review
118 of the available literature, and/or computational toxicology assessment.

119 A TTC concept was developed to define an acceptable intake for unstudied chemicals that may pose a
120 risk of carcinogenicity or other toxic effects. The methods upon which the TTC is based are generally
121 considered to be very conservative since they involve a simple linear extrapolation from the dose
122 giving a 50% tumour incidence (TD_{50}) to a 1 in 10^6 incidence, using TD_{50} data for the most sensitive
123 species and most sensitive site of tumour induction. A dose of 0.0025 µg/kg bw/day was calculated as
124 to be associated with a tumour incidence of 1 in 10^6, and is considered to represent a "virtually safe
125 dose". From a target animal safety perspective, application of a TTC in the assessment of acceptable
126 limits of mutagenic impurities in drug substances and drug products, of 0.025 µg/kg bw/day
127 corresponding to a theoretical 10^{-5} excess lifetime risk of cancer, can be justified. This represents a
128 small theoretical increase in risk when compared to overall lifetime incidence of developing any type of

129 cancer but is acceptable as the animal is expected to receive a health benefit from the medicinal
130 product.

131 Some structural groups have been identified to be of such high potency that intakes even below the
132 TTC would theoretically be associated with a potential for a significant carcinogenic risk. This group of
133 high potency mutagenic carcinogens, referred to as the 'cohort of concern', comprises aflatoxin-like-,
134 N-nitroso-, and alkyl-azoxy compounds.

135 It is noted that established cancer risk assessments are based on lifetime exposures. Less-Than-
136 Lifetime (LTL) exposures can have higher acceptable intakes of impurities and still maintain
137 comparable risk levels.

138 The LTL exposure concept can apply to VMPs for companion animals, but not to those for food-
139 producing animals. For food-producing animals the TTC of 0.025 µg/kg bw/day should not be
140 exceeded, since consumers exposed to residues via food of animal origin are not expected to receive a
141 health benefit and so should not be exposed to levels of relevant impurities above the "virtually safe
142 dose" of 0.0025 µg/kg bw/day. Consumer exposure can be assumed to be below the "virtually safe
143 dose" if the TTC level of 0.025 µg/kg bw/day is respected for the food producing animal as the level of
144 DNA reactive impurities ingested by the consumer will be diluted by a factor of at least 10 compared to
145 the level administered to the target animal.

146 For companion animals, potential justifications for exceeding the TTC of 0.025 µg/kg bw/day may
147 include: treatment of a life-threatening condition, short duration of treatment, limited therapeutic
148 alternatives, or where the impurity is a known substance and exposure will be much greater from other
149 sources.

150 The presence of DNA reactive impurities to which the user may be exposed as a result of treating
151 companion or food producing animals should be addressed as part of the user safety assessment. The
152 appropriate TTC value for use in the user risk assessment is 0.15 µg/day (equivalent to 0.0025 µg/kg
153 bw/day).

154 Where a potential risk has been identified for an impurity, an appropriate control strategy taking into
155 account understanding of manufacturing processes and/or analytical controls should be developed to
156 ensure that the mutagenic impurity is avoided or, if this is technically not possible, is at or below the
157 acceptable level.

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

160 # 5. Considerations for authorised products

161 This guideline is not intended to be applied retrospectively (i.e., to products marketed prior to adoption
162 of this guideline). However, some types of post-approval changes warrant a reassessment of safety
163 relative to mutagenic impurities. This section applies to these post approval changes for products
164 marketed prior to, or after, the adoption of this guideline. Section 9.5 (Lifecycle Management)
165 contains additional recommendations for products marketed after adoption of this guideline.

166 ## 5.1. Post approval changes to the drug substance chemistry,
167 manufacturing, and controls

168 Post approval submissions involving the chemistry, manufacturing, and controls on the drug substance
169 should include an evaluation of the potential risk associated with mutagenic impurities from changes to

170 the route of synthesis, reagents, solvents, or process conditions after the starting material.
171 Specifically, changes should be evaluated to determine if they result in any new mutagenic impurities
172 or higher acceptance criteria for existing mutagenic impurities. Re-evaluation of impurities not
173 affected by changes is not recommended. For example, when only a portion of the manufacturing
174 process is changed, the assessment of risk from mutagenic impurities should be limited to whether any
175 new mutagenic impurities result from the change, whether any mutagenic impurities formed during the
176 affected step are increased, and whether any known mutagenic impurities from up-stream steps are
177 increased. Regulatory submissions associated with such changes should describe the assessment as
178 outlined in Section 10. Changing the site of manufacture of drug substance, intermediates, or starting
179 materials or changing raw materials supplier will not require a reassessment of mutagenic impurity
180 risk.

181 When a new drug substance, intermediate or starting material supplier is proposed, evidence that the
182 substance produced by this supplier uses the same route of synthesis for the substance already used in
183 an existing veterinary medicinal product marketed in the EU is considered to be sufficient evidence of
184 acceptable benefit:risk regarding mutagenic impurities and an assessment per this guideline is not
185 required. If this is not the case, then an assessment per this guideline is expected.

5.2. Post approval changes to the drug product chemistry, manufacturing, and controls

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

5.3. Changes to the clinical use of authorised products

196 Changes to the clinical use of authorised products that can warrant a re-evaluation of the mutagenic
197 impurity limits include: a significant increase in clinical dose, an increase in duration of use, or a
198 change in, or addition of indication, from a serious or life-threatening condition where higher
199 acceptable intakes were justified, to an indication for a less serious condition where the existing
200 impurity acceptable intakes may no longer be appropriate.

5.4. Other considerations for authorised products

202 Application of this guideline to authorised products may be warranted if there is specific cause for
203 concern, for example, if the product contains an impurity with a structure included in the cohort of
204 concern (i.e. high potency mutagenic carcinogens for which the TTC is not sufficiently protective, such
205 as aflatoxin-like-, N-nitroso-, and alkyl-azoxy compounds). However a specific cause for concern would
206 be new relevant hazard data on the impurity (classified as Class 1 or 2, i.e. known mutagenic
207 carcinogens and known mutagens with unknown carcinogenic potential, see Table 1), generated after
208 the overall control strategy and specifications for authorisation were established. This new relevant
209 hazard data should be derived from high-quality scientific studies consistent with relevant regulatory
210 testing guidelines, with data records or reports readily available. Similarly, a newly discovered impurity
211 that is a known Class 1 or Class 2 mutagen that is present in an authorised product could also be a

212 cause for concern. In both of these cases, when the applicant becomes aware of this new information,
213 an evaluation per this guideline should be conducted.

6. Drug substance and veterinary medicinal product impurity assessment

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

219 The impurity assessment is a two-stage process:

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

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

223 The steps as applied to synthetic impurities and degradation products are described in Sections 6.1
224 and 6.2, respectively.

6.1. Synthetic impurities

226 Actual impurities include those observed in the drug substance above the VICH GL10 reporting
227 thresholds. Identification of actual impurities is expected when the levels exceed the identification
228 thresholds outlined by VICH GL10. It is acknowledged that some impurities below the identification
229 threshold may also have been identified.

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

232 The risk of carryover into the drug substance should be assessed for identified impurities that are
233 present in starting materials and intermediates, and impurities that are reasonably expected by-
234 products in the route of synthesis from the starting material to the drug substance. As the risk of
235 carryover may be negligible for some impurities (e.g., those impurities in early synthetic steps of long
236 routes of synthesis), a risk-based justification could be provided, for the point in the synthesis after
237 which these types of impurities should be evaluated for mutagenic potential.

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

241 Actual impurities where the structures are known and potential impurities as defined above should be
242 evaluated for mutagenic potential as described in Section 7.

6.2. Degradation products

244 Actual drug substance degradation products include those observed above the VICH GL10 reporting
245 threshold during storage of the drug substance in the proposed long-term storage conditions and
246 primary and secondary packaging. Actual degradation products in the veterinary medicinal product
247 include those observed above the VICH GL11 reporting threshold during storage of the VMP in the
248 proposed long-term storage conditions and primary and secondary packaging, and also include those
249 impurities that arise during the manufacture of the VMP. Identification of actual degradation products
250 is expected when the levels exceed the identification thresholds outlined by VICH GL 10/11. It is

251 acknowledged that some degradation products below the identification threshold may also have been
252 identified.

253 Potential degradation products in the drug substance and VMP are those that may be reasonably
254 expected to form during long term storage conditions. Potential degradation products include those
255 that form above the VICH GL 10/11 identification threshold during accelerated stability studies (e.g.,
256 40°C/75% relative humidity for 6 months), but are yet to be confirmed in the drug substance or VMP
257 under long-term storage conditions in the primary packaging.

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

261 Actual and potential degradation products likely to be present in the final drug substance or VMP, and
262 where the structure is known, should be evaluated for mutagenic potential as described in Section 7.

7. Hazard assessment elements

264 Hazard assessment involves an initial analysis of actual and potential impurities by conducting
265 database and literature searches for carcinogenicity and bacterial mutagenicity data in order to classify
266 them as Class 1, 2, or 5 according to Table 1. If data for such a classification are not available, an
267 assessment of Structure-Activity Relationships (SAR) that focuses on bacterial mutagenicity predictions
268 should be performed. This could lead to a classification into Class 3, 4, or 5.

269 **Table 1.** Impurities Classification with Respect to Mutagenic and Carcinogenic Potential and Resulting
270 Control Actions

Class	Definition	Proposed action for control (details in Section 8 and 9)
1	Known mutagenic carcinogens	Control at or below compound-specific acceptable limit
2	Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive*, no rodent carcinogenicity data)	Control at or below acceptable limits (appropriate TTC)
3	Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data	Control at or below acceptable limits (appropriate TTC) or conduct bacterial mutagenicity assay; If non-mutagenic = Class 5 If mutagenic = Class 2
4	Alerting structure, same alert in drug substance or compounds related to the drug substance (e.g., process intermediates) which have been tested and are non-mutagenic	Treat as non-mutagenic impurity
5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity	Treat as non-mutagenic impurity

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

273 A computational toxicology assessment should be performed using (Q)SAR methodologies that predict
274 the outcome of a bacterial mutagenicity assay (Ref.1). Two (Q)SAR prediction methodologies that
275 complement each other should be applied. One methodology should be expert rule-based and the
276 second methodology should be statistical-based. (Q)SAR models utilizing these prediction
277 methodologies should follow the general validation principles set by the Organisation for Economic Co-
278 operation and Development (OECD).

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

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

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

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

301 8. Risk characterization

302 As a result of the hazard assessment described in Section 7, each impurity will be assigned to one of
303 the five classes in Table 1. For impurities belonging in Classes 1, 2, and 3, the principles of risk
304 characterization used to derive acceptable intakes are described in this section.

305 8.1. TTC-based acceptable intakes

306 From the point of view of target animal safety, a TTC-based acceptable intake of a mutagenic impurity
307 of 0.025 µg/kg bw per day is considered to be associated with a negligible risk and would usually be
308 used for mutagenic impurities present in VMPs intended for long-term treatment and where no
309 carcinogenicity data are available (Classes 2 and 3).

8.2. Acceptable intakes based on compound-specific risk assessments

8.2.1. Mutagenic impurities with positive carcinogenicity data (class 1 in table 1)

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

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.

8.2.2. 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 is based on calculation of a permitted daily exposure.

The permitted daily exposure (PDE) is preferably derived from the No-Observed Adverse Effect Level (NO(A)EL) in the most relevant animal study. The modifying (uncertainty) factors comprise factors to account for e.g. extrapolation between species, variability between individuals, and/or short-term toxicological studies (as described in VICH GL18, Appendix 3), (Ref.2).

8.3. Acceptable intakes in relation to less-than-lifetime (LTL) exposure for companion animals

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

The TTC-based acceptable intake of 0.025 µg/kg bw/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 is uniformly distributed over the total number of exposure days during LTL exposure. This would allow higher daily intake of mutagenic impurities than would be the case for lifetime exposure and still maintain comparable risk levels for daily and non-daily treatment regimens.

The LTL concept can only be applied for companion animals. However, the approach described in the ICH M7 (Ref. 6) guideline uses an estimated human lifespan of 70 years. A parallel approach cannot be directly applied to companion animals due to the large variety of their life expectancies. If the applicant proposes increased acceptable intakes of mutagenic impurities for limited treatment periods then a scientifically justified description of how the LTL concept is used will be required.

The LTL approach is not accepted for food producing animals as, for substances administered to these animals, consideration needs to be given to potential consumer exposure to residues, which could be chronic even if target animal exposure is for only a short duration.

8.4. Acceptable intakes for multiple mutagenic impurities

The TTC-based acceptable intakes should be applied to each individual impurity. When more than one genotoxic impurity is present in the drug substance, the TTC value can be applied to each individual impurity only if the impurities are structurally unrelated. In case of structural similarity the same genotoxic mode of action is assumed and therefore the sum of impurities must not exceed the TTC.

8.5. Exceptions and flexibility in approaches

For impurities present in VMPs for food producing animals, as a matter of principle, since consumers exposed to residues via food of animal origin have no health benefit, the standard TTC may not be exceeded. Potential exceptions require a profound justification by the applicant.

For impurities present in VMPs for use in companion animals possible reasons for departing from the standard approach might include:

- Higher acceptable intakes may be justified when 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 may be justified in cases of severe disease, reduced life expectancy or where there are limited therapeutic alternatives.

- Compounds from some structural classes of mutagens can display extremely high carcinogenic potency (cohort of concern), i.e., aflatoxin-like-, N-nitroso-, and alkyl-azoxy structures. Intakes even below the TTC are theoretically associated with a potential for a significant carcinogenic risk and a case-by-case approach using e.g., carcinogenicity data from closely related structures, if available, should usually be developed to justify acceptable intakes for authorised VMPs.

- Where available data were generated using a route of administration other than that by which the product will be administered, consideration will need to be given to the validity of any conclusions.

9. Control[1]

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

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

- Facility and equipment operating conditions;

- Controls implicit in the design of the manufacturing process;

- In-process controls (including in-process tests and process parameters);

- Controls on drug substance and drug product (e.g., release testing).

When an impurity has been characterized as Classes 1, 2, or 3 in Table 1, it is important to develop a control strategy that assures that the level of this impurity in the drug substance and drug product is below the acceptable limit. A thorough knowledge of the chemistry associated with the drug substance

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[1] Several references to ICH documents are included in the guideline. Whilst veterinary products are outside the scope of these ICH documents there are no corresponding VICH documents and the principles outlined in these ICH documents may also be relevant to veterinary products. By inclusion of these references it is not the intention to introduce any additional requirements for veterinary products, on the contrary they are included in order to facilitate flexibility and to allow the applicant the option of using different approaches.

386 manufacturing process, and of the drug product manufacturing process, along with an understanding
387 of the overall stability of the drug substance and drug product is fundamental to developing the
388 appropriate controls. Developing a strategy to control mutagenic impurities in the drug product is
389 consistent with risk management processes principles identified in ICH Q9 (Ref.3). A control strategy
390 that is based on product and process understanding and utilisation of risk management principles will
391 lead to a combination of process design and control and appropriate analytical testing, which can also
392 provide an opportunity to shift controls upstream and minimize the need for end-product testing.

9.1. Control of process related impurities

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

395 **Option 1**

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

398 For an Option 1 control approach, it is possible to apply periodic testing per VICH GL39 (Ref 4).
399 Periodic verification testing is justified when it can be shown that levels of the mutagenic impurity in
400 the drug substance are less than 30% of the acceptable limit for at least 6 consecutive pilot scale or 3
401 consecutive production scale batches. If this condition is not fulfilled, a routine test in the drug
402 substance specification is recommended. See Section 9.3 for additional considerations.

403 **Option 2**

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

407 **Option 3**

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

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

417 **Option 4**

418 Understand process parameters and impact on residual impurity levels (including fate and purge
419 knowledge) with sufficient confidence that the level of the impurity in the drug substance will be below
420 the acceptable limit such that no analytical testing is recommended for this impurity. (i.e., the impurity
421 does not need to be listed on any specification).

422 A control strategy that relies on process controls in lieu of analytical testing can be appropriate if the
423 process chemistry and process parameters that impact levels of mutagenic impurities are understood
424 and the risk of an impurity residing in the final drug substance above the acceptable limit is
425 determined to be negligible. In many cases justification of this control approach based on scientific
426 principles alone is sufficient. Elements of a scientific risk assessment can be used to justify an option 4

427 approach. The risk assessment can be based on physicochemical properties and process factors that
428 influence the fate and purge of an impurity including chemical reactivity, solubility, volatility,
429 ionizability and any physical process steps designed to remove impurities. The result of this risk
430 assessment might be shown as an estimated purge factor for clearance of the impurity by the process
431 (Ref. 5).

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

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

9.2. Considerations for control approaches

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

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

456 The application of "As Low As Reasonably Practicable" (ALARP) is not necessary if the level of the
457 mutagenic impurity is below acceptable limits. Similarly, it is not necessary to demonstrate that
458 alternate routes of synthesis have been explored.

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

9.3. Considerations for periodic testing

463 The above options include situations where a test is recommended to be included in the specification,
464 but where routine measurement for release of every batch may not be necessary. This approach,
465 referred to as periodic or skip testing in VICH GL39 could also be called "Periodic Verification Testing."
466 This approach may be appropriate when it can be demonstrated that processing subsequent to
467 impurity formation/introduction clears the impurity. It should be noted that allowance of Periodic
468 Verification Testing is contingent upon use of a process that is under a state of control (i.e., produces a
469 quality product that consistently meets specifications and conforms to an appropriately established

470 facility, equipment, processing, and operational control regimen). If upon testing, the level of the
471 mutagenic impurity fails to meet the acceptance criteria established for the periodic test, the drug
472 producer should immediately commence full testing (i.e., testing of every batch for the attribute
473 specified) until the cause of the failure has been conclusively determined, corrective action has been
474 implemented, and the process is again documented to be in a state of control. As noted in VICH GL39,
475 regulatory authorities should be notified of a periodic verification test failure to evaluate the
476 benefit/risk of previously released batches that were not tested.

9.4. Control of degradation products

478 For a potential degradation product that has been characterized as mutagenic, it is important to
479 understand if the degradation pathway is relevant to the drug substance and drug product
480 manufacturing processes and/or their proposed packaging and storage conditions. A well-designed
481 accelerated stability study (e.g., 40 $^\circ$C/75% relative humidity, 6 months) in the proposed packaging,
482 with appropriate analytical procedures is recommended to determine the relevance of the potential
483 degradation product. Alternatively, well designed kinetically equivalent shorter term stability studies
484 at higher temperatures in the proposed commercial package may be used to determine the relevance
485 of the degradation pathway prior to initiating longer term stability studies. This type of study would be
486 especially useful to understand the relevance of those potential degradation products that are based on
487 knowledge of potential degradation pathways but not yet observed in the product.

488 Based on the result of these accelerated studies, if it is anticipated that the degradation product will
489 form at levels approaching the acceptable limit under the proposed packaging and storage conditions,
490 then efforts to control formation of the degradation product are expected. In these cases, monitoring
491 for the drug substance or drug product degradation product in long term primary stability studies at
492 the proposed storage conditions (in the proposed commercial pack) is expected unless otherwise
493 justified. Whether or not a specification limit for the mutagenic degradation product is appropriate will
494 generally depend on the results from these stability studies.

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

9.5. Lifecycle management

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

500 Quality system elements and management responsibilities such as those described in ICH Q10 (Ref 7)
501 are intended to encourage the use of science-based and risk-based approaches at each lifecycle stage,
502 thereby promoting continual improvement across the entire product lifecycle. Product and process
503 knowledge should be managed from development through the commercial life of the product up to and
504 including product discontinuation.

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

510 Any proposed change to the manufacturing process should be evaluated for the impact on the quality
511 of drug substance and drug product. This evaluation should be based on understanding of the
512 manufacturing process and should determine if appropriate testing to analyze the impact of the

513 proposed changes is required. Additionally, improvements in analytical procedures may lead to
514 structural identification of an impurity. In those cases the new structure would be assessed for
515 mutagenicity as described in this guideline.

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

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

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

10. Documentation

529 • Information relevant to the application of this guideline should be provided. For actual and
530 potential process related impurities and degradation products where assessments according to this
531 guideline are conducted, the mutagenic impurity classification and rationale for this classification
532 should be provided:

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

536 – When bacterial mutagenicity assays were performed on impurities, study reports should be
537 provided.

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

Notes

Note 1 This Guideline provides an approach for assessing the potential of impurities to induce point mutations and ensure that such impurities are controlled to safe levels so that below the VICH GL10/11 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 the qualification threshold in VICH GL10, evaluation of genotoxic potential as recommended in VICH GL10 should be considered, with any impurity found to be positive in genotoxicity tests removed, reduced to a safe level (if a level can be identified), or reduced to levels that are compliant with the recommendations in this guideline (ie exposure ≤ TTC). In cases where the identified impurities are present at less than the qualification threshold, qualification should be undertaken in line with the guidance provided in this document.

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 VICH GL23(R) and OECD 471 guidelines (Ref.8, 9,). The assays are expected to be performed in compliance with Good Laboratory Practices (GLP) regulations. Any deviations should be described in the study report. For example, the test article may not be prepared or analyzed in compliance with GLP regulations. In some cases, the selection of bacterial tester strains may be limited to those proven to be sensitive to the identified alert. For impurities that are not feasible to isolate or synthesize, or when compound quantity is limited, it may not be possible to achieve the highest test concentrations recommended for a VICH-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 VICH-compliant assay to enable testing at higher concentrations with justification.

Glossary

Acceptable intake:

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

Acceptable limit:

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

Acceptance criterion:

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

Control strategy:

A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and VMP 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 an animal is exposed to over time.

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

DNA-reactive:

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

Expert knowledge:

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

Genotoxicity:

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

Impurity:

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

Mutagenic impurity:

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

(Q)SAR and SAR:

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

607 **Purge factor:**

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

611 **Structural alert:**

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

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References

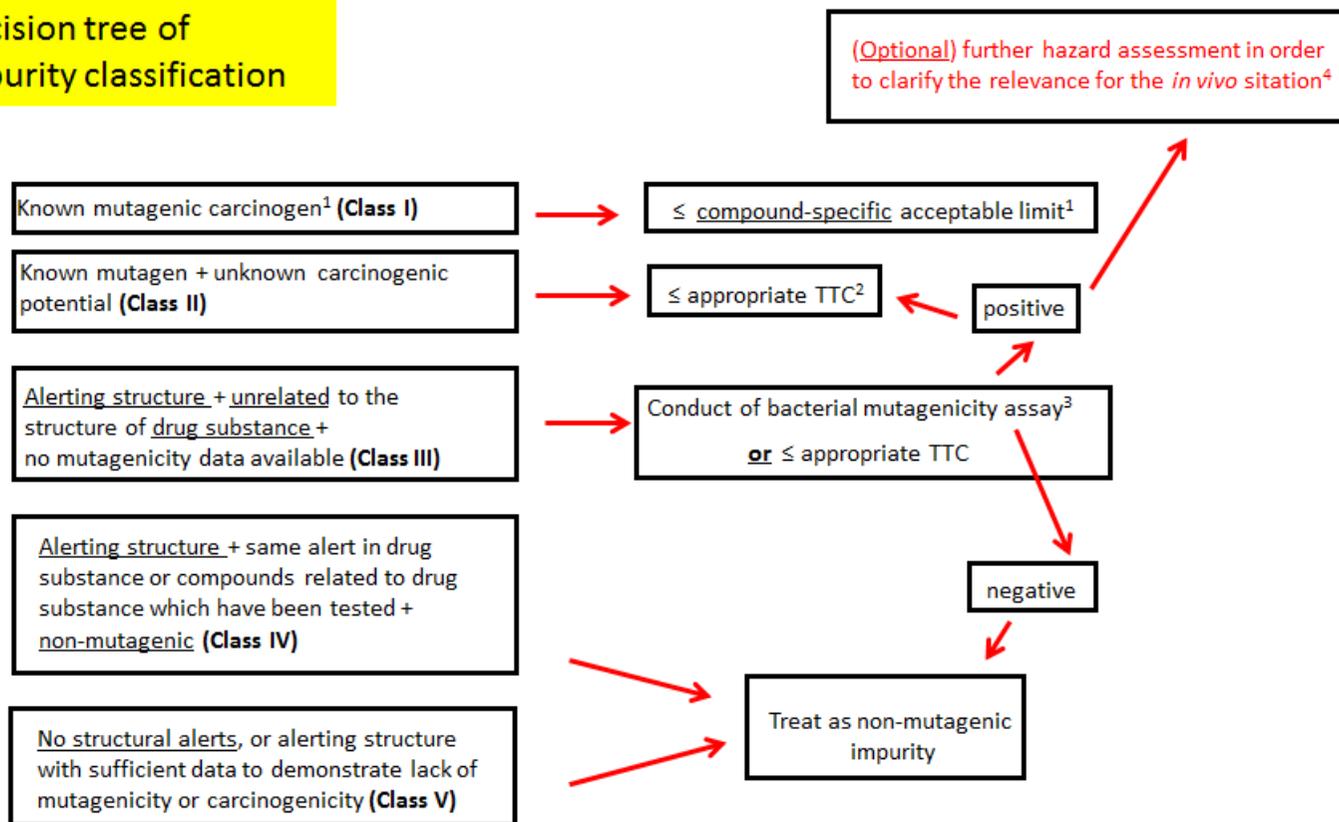1. Sutter A, Amberg A, et al (2013). Use of in silico systems and expert knowledge for structure-based assessment of potentially mutagenic impurities. Regul Toxicol Pharmacol 2013 67:39-52.

2. VICH GL 18(R): Impurities: Residual solvents in new veterinary medicinal products, active substances and excipients (Revision) (EMA/CVMP/VICH/502/99-Rev.1)

3. International Conference on Harmonisation (2005). Q9: Quality Risk Management.

4. VICH Topic GL39 (2005), guideline on test procedures and acceptance criteria for new veterinary drug substances and new medicinal products: chemical substances (VICH Topic GL39)

5. Teasdale A., Elder D., Chang S-J, Wang S, Thompson R, Benz N, Sanchez Flores I, (2013). Risk assessment of genotoxic impurities in new chemical entities: strategies to demonstrate control. Org Process Res Dev 17:221−230.

6. International Conference on Harmonisation (2014). M7: Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk

7. International Conference on Harmonisation (2008). Q10: Pharmaceutical Quality System.

8. VICH GL 23(R): Studies to evaluate the safety of residues of veterinary drugs in human food: genotoxicity testing (EMA/CVMP/VICH/526/2000)

9. Test 471. Bacterial Reverse Mutation Test OECD Guideline for Testing of Chemicals Section 4 1997 July

633   **Appendix 1: Decision tree**

634

Decision tree of impurity classification

(Optional) further hazard assessment in order to clarify the relevance for the *in vivo* sitation[4]

Known mutagenic carcinogen[1] **(Class I)** → ≤ compound-specific acceptable limit[1]

Known mutagen + unknown carcinogenic potential **(Class II)** → ≤ appropriate TTC[2] ← positive

Alerting structure + unrelated to the structure of drug substance + no mutagenicity data available **(Class III)** → Conduct of bacterial mutagenicity assay[3] **or** ≤ appropriate TTC

Alerting structure + same alert in drug substance or compounds related to drug substance which have been tested + non-mutagenic **(Class IV)**

negative

No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity **(Class V)** → Treat as non-mutagenic impurity

[1] For class I, a compound-specific acceptable intake can be calculated based on carcinogenic potency and linear extrapolation as a default approach, see chapter 8.2.1.
[2] TTC = 0.025 µg/kg bw;
[3] bacterial mutagenicity assay or (Q)SAR methodologies that predict the outcome of a bacterial mutagenicity assay
[4] For instance, when levels of the impurity cannot be controlled at an appropriate acceptable limit, it is recommended that the impurity be tested in an in vivo gene mutation assay in order to understand the relevance of the bacterial mutagenicity assay result under in vivo conditions.

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Appendix 2: Scope scenarios for application of the guideline

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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
A new formulation of an approved drug substance is filed	No	Yes	See Section 5.2
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 reevaluation of mutagenic impurity risk is not necessary. The applicant would need to demonstrate that no changes have been made to a previously approved process/product. Refer to Section 5.1.
New combination product is filed that contains one new drug substance and an existing drug substance	Yes (new drug substance) No (existing drug substance)	Yes	The guideline would apply to the new drug substance. For the existing drug substance, retrospective application of the 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 degradation products.

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Appendix 3: Case examples to illustrate potential control approaches

Case 1: Example of an option 3 control strategy

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

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

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

Case 3: Example of an option 2 and 4 control strategy: control of structurally similar mutagenic impurities

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

682 **Case 4: Example of an option 4 control strategy: highly reactive impurity**

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