



1 18 January 2013
2 EMA/CVMP/SWP/398880/2012
3 Committee for Medicinal Products for Veterinary Use (CVMP)

4 **Concept paper for a guideline on limits for genotoxic**
5 **impurities**

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| Agreed by Safety Working Party | September 2012 |
| Adoption by CVMP for release for consultation | 10 January 2013 |
| Start of public consultation | 18 January 2013 |
| End of consultation (deadline for comments) | 30 April 2013 |

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Comments should be provided using this [template](#). The completed comments form should be sent to vet-guidelines@ema.europa.eu

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9 **1. Introduction**

10 The risk assessment related to the presence of impurities in veterinary medicinal products should be
11 based on recommendations from VICH GL10 (guideline on impurities in new veterinary drug
12 substances), VICH GL11 (guideline on impurities in new veterinary medicinal products) and VICH GL18
13 (residual solvents in veterinary medicinal products, active substances and excipients) where more
14 specific information relating to residual solvents is available. As described in these guidelines, the
15 qualification of the impurities is the process of acquiring and evaluating data that establishes the safety
16 of an individual impurity or a given impurity profile at the level specified. For impurities with genotoxic
17 potential, the need for the determination of acceptable dose levels corresponds to a specific issue,
18 which is not completely covered by the currently adopted guidelines.

19 **2. Problem statement**

20 The presence and the toxicological assessment of potentially genotoxic impurities in active substances
21 and in finished product is an important issue which has been the subject of discussion for several
22 years.

23 While it is preferable to avoid the presence of genotoxic impurities, it is acknowledged that it is not
24 possible to entirely avoid the presence of impurities with genotoxic potential in all veterinary medicinal
25 products (VMPs). At present there is no veterinary guidance on how to address the presence of such
26 impurities, and this can be the cause of difficulties in assessments of marketing authorisation
27 applications.

28 For human medicines, since the determination of acceptable dose levels was not specifically covered by
29 the guidelines on the qualification of impurities for human medicines (ICH Q3A and Q3B), the
30 Committee for Medicinal Products for Human Use (CHMP) has developed the "Guideline on the limits of
31 genotoxic impurities" (CHMP/SWP/5199/02, EMEA/CHMP/QWP/251344/2006), which came into effect
32 on 1 January 2007.

33 It is expected that the scope of the veterinary guideline will be similar to what which was agreed on
34 the human side.

35 **3. Discussion (on the problem statement)**

36 In absence of guidance for veterinary medicinal products, the intention is, as a first step, to explore
37 whether the approach used in the CHMP guideline on genotoxic impurities (CPMP/SWP/5199/02) could
38 be applied on the veterinary side.

39 As described in the CHMP guidance, based on available genotoxicity data or on the presence of
40 structural alerts, potentially genotoxic impurities should be identified. Additional genotoxicity testing is
41 to be considered.

42 For genotoxic compounds with sufficient evidence of a threshold-related mechanism of action, the
43 CHMP approach requires the calculation of a permitted daily exposure (PDE) and a margin of exposure
44 (MOE). This approach appears directly transferable to the risk assessment of these impurities for
45 companion animals, for food producing animals and, as a secondary exposure, for consumers.

46 For genotoxic compounds without sufficient evidence of a threshold-related mechanism, where no MOE
47 can be defined, the CHMP approach is to compare the expected patient exposure to a threshold of
48 toxicological concern (TTC). This approach may also be directly applicable when considering target
49 animal safety (for companion and food producing animals). It should be noted that VMPs can be

50 considered to offer a health benefit for target animals, and this should be taken into account when
51 selecting the TTC. A TTC of 1.5 µg/person/day (0.025 µg/kg bw) is used in the CHMP guideline and a
52 comparable figure may be appropriate when considering target animal safety. In the case of food
53 producing animals, consumers may experience secondary exposure to residues of VMPs, and for the
54 consumer it can be considered that there is no direct health benefit resulting from this exposure.
55 Consideration will be given to the possibility of using a TTC value when considering consumer safety.
56 However, this will require estimation of the exposure of the consumer. Distribution, metabolism and
57 excretion of impurities in target animals should also be considered in order to refine the exposure level
58 expected in consumers.

59 It is also noted that ICH is in the process of developing guidance on the assessment and control of
60 DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk. The
61 appropriateness and relevance of the approaches recommended in the draft ICH guidance, when
62 published for consultation, will be considered.

63 **4. Recommendation**

64 In absence of guidance on limits for genotoxic impurities in veterinary medicinal products, the CVMP
65 recommends the development of a guideline to describe a practical approach on how to deal with
66 genotoxic impurities, taking account of both target animals and consumer safety. This document will
67 have to define the type of information required for assessment and how to perform the risk
68 assessment according to the type of genotoxic impurities.

69 **5. Proposed timetable**

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| 70 | 30 April 2013 | Deadline for comments |
| 71 | May - September 2013 | Pending comments received SWP develops a draft guideline |
| 72 | September - December 2013 | Consultation with EWP and QWP |
| 73 | January 2014 | CVMP adopts the draft guideline for release for 6 months consultation |
| 74 | 31 July 2014 | Deadline for comments |
| 75 | August –February 2014 | SWP develops final guideline |
| 76 | March – April 2015 | Consultation with EWP and QWP |
| 77 | June 2015 | CVMP adopts the final guideline |

78 **6. Resource requirements for preparation**

79 It is proposed that the SWP develops the guideline. A Rapporteur and Co-rapporteur will be nominated.
80 Adequate time for discussions at the SWP will be required and EWP and QWP will be required to
81 comment on the proposals from SWP. The EMA secretariat will coordinate the consultation and
82 communication between the working parties as well as the public consultation. Time at plenary CVMP
83 will be required to discuss and adopt the various drafts of the guideline.

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85 **7. Impact assessment (anticipated)**

86 **Impact for Industry and other Interested Parties**

87 The guideline should be beneficial for industry by clarifying the studies necessary with regard to the
88 risk assessment related to the presence of genotoxic impurities in veterinary medicinal products.

89 **Impact assessment for regulatory authorities**

90 The guideline should be beneficial for regulatory authorities as it will describe a practical approach on
91 how to deal with genotoxic impurities in veterinary medicinal products.

92 **8. Interested parties**

93 Consumers, regulators, veterinary medicines industry.

94 **9. References to literature, guidelines, etc.**

95 VICH Topic GL 10 Guideline on impurities in new veterinary drug substances
96 (EMA/CVMP/VICH/837/99-Rev.1)

97 VICH Topic GL 11 Guideline on impurities in new veterinary medicinal products
98 (EMA/CVMP/VICH/838/99-Rev.1)

99 VICH GL18(R) Impurities: Residual solvents in new veterinary medicinal products, actives substances
100 and excipients (Revision)

101 CHMP Guideline on the limits of genotoxic impurities (EMA/CHMP/QWP/251344/2006).