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Committee for Human Medicinal Products (CHMP)

# Concept paper on a Proposal to limit the applicability of the CPMP/CVMP Note for Guidance on Limitations to the Use of Ethylene Oxide in the Manufacture of Medicinal Products (CPMP/QWP/159/01) to veterinary medicinal products

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The proposed guideline will replace 'Note for Guidance on Limitations to the Use of Ethylene Oxide in the Manufacture of Medicinal Products' (CPMP/QWP/159/01).

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| **Keywords** | ***Ethylene Oxide, DNA-reactive, class 1 impurities, acceptable limits, genotoxic impurities, medicinal products*** |

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# 1. Introduction

In 2001 the Agency released the CPMP/CVMP Note for Guidance on Limitations to the Use of Ethylene Oxide in the Manufacture of Medicinal Products. Ethylene oxide is a highly reactive compound and is used in the synthesis of pharmaceutical raw materials and as a sterilant. Ethylene oxide is considered carcinogenic to humans (IARC group 1) based on sufficient evidence from animal studies for carcinogenicity and compelling data in support of a genotoxic mode of action. In view of this potential the Note for Guidance stipulates that the use of ethylene oxide in the manufacture of medicinal products "is acceptable only when pharmaceutically absolutely necessary and then residual ethylene oxide in the product should not exceed a limit of 1 ppm". This limit is based on analytical feasibility rather than toxicological considerations; 1 ppm was considered the limit of detection for ethylene oxide residues at the time the Guideline was released.

# 2. Problem statement

The recently adopted ICH M7 Guideline 'Assessment and Control of DNA-Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk' (2014) is recommending a knowledge-based risk assessment to define acceptable intake levels for impurities that are known mutagenic carcinogens. Using the ICH-approach results in acceptable limits for ethylene oxide that are in clear conflict with the limits set by the EU Note for Guidance.

The ICH guidance does not apply to veterinary medicinal products and consequently, for these products, the only applicable guidance with relevance to limits for ethylene oxide remains the CPMP/CVMP Note for Guidance on Limitations to the Use of Ethylene Oxide in the Manufacture of Medicinal Products.

# 3. Discussion (on the problem statement)

The EU Guideline on the Limits of Genotoxic Impurities (2007) and more so the ICH M7 Guideline (2014) have led to a regulatory paradigm shift towards a toxicologically defined acceptance of low levels of DNA reactive carcinogens in lieu of a control policy based on ALARP principle and analytical capabilities. For mutagenic impurities with carcinogenicity data like ethylene oxide (so-called Class 1 impurities) ICH M7 is recommending a compound-specific approach in setting acceptable intake limits based on carcinogenic potency data (TD50-values). A 50.000-fold linear extrapolation down from the lowest compound-specific TD50-value results in a daily acceptable intake (AI) corresponding to a less than 1 in 100000 upper bound lifetime risk of cancer. This human intake level is considered to pose a negligible risk of carcinogenicity.

In ICH M7, Note 4, rodent carcinogenicity data of ethylene oxide are used as an example to illustrate this approach. The resulting daily AI is 21.3 µg ethylene oxide corresponding to a 1 x 10-5 cancer risk level. For a daily therapeutic dose of a drug substance of, for instance, 100 mg this specific AI results in a maximum allowable concentration of ethylene oxide as an impurity in the drug substance of 210 ppm. Thus, the ICH M7-derived acceptable limit is considerably higher than the maximum limit of 1 ppm as requested by the EU Note for Guidance (EMEA 2001).

# 4. Recommendation

SWP is recommending to withdraw the Note for Guidance on Limitations to the Use of Ethylene Oxide in the Manufacture of Medicinal Products and replace the guidance provided for the limitation of ethylene oxide by the approach that is recommended for Class 1 impurities in ICH M7. This recommendation applies to medicinal products for human use only.

For veterinary medicinal products the CPMP/CVMP Note for Guidance on Limitations to the Use of Ethylene Oxide in the Manufacture of Medicinal Products will continue to apply[1].

# 5. References to literature, guidelines, etc.

Note for Guidance on limitations to the use of Ethylene Oxide in the manufacture of medicinal products (CPMP/QWP/159/01)

ICH M7 Guideline: Assessment and Control of DNA-Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (2014)

[1] The CVMP SWP is currently developing guidance relating to genotoxic impurities in veterinary medicinal products. Once available, this guidance may allow the withdrawal of the CPMP/CVMP Note for Guidance on Limitations to the Use of Ethylene Oxide in the Manufacture of Medicinal Products for veterinary medicinal products also.