



The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

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**COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)
COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS (CVMP)**

**NOTE FOR GUIDANCE ON LIMITATIONS TO THE USE OF
ETHYLENE OXIDE IN THE MANUFACTURE OF MEDICINAL
PRODUCTS**

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NOTE FOR GUIDANCE ON LIMITATIONS TO THE USE OF ETHYLENE OXIDE IN THE MANUFACTURE OF MEDICINAL PRODUCTS

This note for guidance deals with the use of ethylene oxide in pharmaceutical raw materials, finished products and containers.

1. TOXICOLOGICAL BACKGROUND

Ethylene oxide is a substance which, due to its structure, is counted among the very reactive compounds. This reactivity also includes organic structures within cells and cell nuclei. In this case, alkylation and reactions with DNA, RNA and proteins occur. Cytotoxicity, carcinogenicity and mutagenicity of ethylene oxide, which have been demonstrated by many in vitro and in vivo tests, are attributed to these properties.

Epidemiological data from many sources indicates that workers exposed to ethylene oxide at their work place had an increased incidence of leukaemia and other tumours.

In view of the known positive potential of ethylene oxide for genotoxic carcinogenicity, it is recommended that use 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 the current limit of detection for ethylene oxide residues.

Any deviation upwards from this limit must be justified with supporting data and defended, taking into account the clinical risk/benefit assessment for the particular products under consideration.

2. CATEGORIES OF USE OF ETHYLENE OXIDE

Ethylene oxide is used in the synthesis of pharmaceutical raw materials and as a sterilant. Since it is effective only as a surface sterilant it should be used only when justified and validated on an individual basis.

Ethylene oxide sterilisation should be used only where safer alternatives cannot be used. For containers filled with aqueous products, e.g. pre-filled syringes, the need for a justification for the use of ethylene oxide in the sterilisation of the container prior to filling can be waived provided the container itself fulfills the specification listed under 3.3 as the degradation kinetics of ethylene oxide in an aqueous medium have been sufficiently demonstrated.

3. SPECIFICATIONS/TEST PROCEDURES

Due to the above mentioned considerations, the limits are fixed on a mass/mass basis and not on a daily intake basis. If no official test procedure (e.g. Pharmacopoeia) is available a validated test procedure must be proposed by the applicant (see also note for guidance on Validation of Analytical Procedures: Methodology).

3.1 Raw materials

Specification:

Ethylene oxide: 1 µg/g

Ethylene chlorhydrin (or any other halogenated ethylenehydrine): 50 µg/g.

3.2 Finished product

If the residual ethylene oxide originates from its use in the raw starting material, its content must be limited in the raw starting material.

Specification (when used on the finished product):

Ethylene oxide: 1 µg/g

Ethylene chlorhydrin (or any other halogenated ethylenehydrine): 50 µg/g.

3.3 Containers

Specification (based on simulated use):

Ethylene oxide: 1 µg/ml (container volume)

Ethylene chlorhydrin (or any other halogenated ethylenehydrine): 50 µg/ml (container volume).