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Committee for medicinal products for human use (CHMP)
Committee for medicinal products for veterinary use (CVMP)

Annexes to:
CPMP/ICH/283/95 Impurities: Guideline for residual solvents &
CVMP/VICH/502/99 Guideline on impurities: residual solvents

Annex I: specifications for class 1 and class 2 residual solvents in active substances

Annex II: residues of solvents used in the manufacture of finished products

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Annexes to: CPMP/ICH/283/95 Impurities: Guideline for residual solvents & CVMP/VICH/502/99 Guideline on impurities: residual solvents

Introduction

The two (V)ICH residual solvents guidelines, ICH Q3C Impurities: Guideline for residual solvents (CPMP/ICH/283/95) and VICH GL18 Guideline on impurities: residual solvents in new veterinary medicinal products, active substances and excipients (CVMP/VICH/502/99), have been in operation for several years, since March 1998 and June 2001 respectively.

However, it has become evident that further clarification was required regarding the specifications for Class 1 and class 2 residual solvents in active substances.

A clear interpretation of the issues regarding residues of solvents used in the manufacture of finished medicinal products, both human and veterinary, was also required.

Annex I: Specifications for class 1 and class 2 residual solvents in active substances

Specifications for class 1 solvents

In both the ICH and VICH guidelines on impurities: residual solvents it is stated that “solvents in class 1 should not be employed in the manufacture of drug/active substances, excipients, and drug/veterinary medicinal products because of their unacceptable toxicity or their deleterious environmental effect. However, if their use is unavoidable in order to produce a drug/veterinary medicinal product with a significant therapeutic advance, then their levels should be restricted as shown....., unless otherwise justified”.

The justification for using a class 1 solvent as a solvent in a manufacturing process may be based on the current scientific and technical knowledge and the step in which this solvent is involved. For example, use of that class 1 solvent is unavoidable for the specific chemical reaction, or the desired purity profile can only be obtained by using that class 1 solvent. If a class 1 solvent is involved in a very early step of the manufacturing process and if the absence of this solvent is shown in a suitable intermediate, such an approach may be acceptable (for example, Friedel-Crafts chemical reaction).

The maximum acceptable limit, in a suitable intermediate or in the final active substance, for a class 1 solvent, whether it is used as a solvent, a starting material, is present as a by-product, or it is present in a solvent, should comply with the limits prescribed in the relevant aforementioned ICH/VICH guideline on impurities: residual solvents, unless otherwise justified (for example, by the benefit:risk ratio).

In all cases, the content of class 1 solvents in the final active substance should comply with the requirements of the relevant aforementioned Guideline, if tested.

A class 1 solvents used as starting materials

Certain class 1 solvents, such as benzene and 1,2-dichloroethane, can be used as starting materials.

Indeed, the use of benzene as a starting material is unavoidable when benzene is a structural part of the active substance.

Benzene, as a starting material, is commonly used in the very early steps of syntheses, well before the key starting material obtained. It is the reason why, in most cases benzene is not mentioned in the description of the manufacturing process. Therefore a manufacturer describing a synthesis starting from benzene should not be asked to eliminate it when another manufacturer could refer to a synthetic route starting from a later process step (where no questions related to the use of this class 1 solvent would be raised).

When class 1 solvents are used as starting materials they should be routinely controlled, either in a suitable intermediate or in the final active substance.

B class 1 solvents present as an impurity

Benzene in an active substance can be a by-product from a chemical reaction (for example, grignard reaction, when phenylmagnesium halide used in excess is hydrolysed to yield benzene), or may arise from another solvent, for example, toluene or acetone where benzene is a known process impurity.

Where a class 1 solvent might be present in another solvent (e.g. toluene or acetone containing benzene), a routine test for this class 1 solvent, on a suitable intermediate or on the final active substance, is not required when:

- The limit applied to the originator solvent is such that the class 1 solvent will be present in the active substance at levels below the limits set out in the guideline, taking into account the maximum likely level of contamination of the class 1 solvent. The volatility of both solvents in the drying processes must be taken into account when applying this argument;
- It is demonstrated with a validated method that the class 1 solvent is not more than 30 % of the specified limit, in a suitable intermediate or in the final active substance. Supporting data should be presented on 6 consecutive pilot scale batches or 3 consecutive industrial scale batches;
- The specification for the originator solvent used includes a routinely performed test and limit for the class 1 solvent.

Specifications for class 2 solvents

When class 2 solvents are used as starting materials or solvents, they should be normally routinely controlled either in a suitable intermediate or in the final active substance depending on the step(s) of the syntheses in which they are used.

The limit set for class 2 solvents in the final active substance should comply with the requirements of the relevant aforementioned ICH/VICH guideline on impurities: residual solvents.

A class 2 solvents used in the last step of the synthesis

In all cases where a class 2 solvent is used in the last step of a synthesis it should be routinely controlled in the final active substance.

B class 2 solvents used prior to the last step of the synthesis

Class 2 solvents used prior to the last step in the synthesis have not to be included in the drug substance specification if it has been demonstrated, on a suitable intermediate or on the final active substance, that the content of class 2 solvents is not more than 10 % of the acceptable concentration limit (e.g., acetonitrile 41 ppm) stated in the relevant aforementioned ICH/VICH guideline on impurities: residual solvents. If tested, the content of class 2 solvents in the final active substance should of course meet the requirements of the relevant aforementioned guideline.

To support the absence of a routine test for class 2 solvents in the final active substance or in the suitable intermediate, results of the content of class 2 solvents should be presented from 6 consecutive pilot scale batches or 3 consecutive industrial scale batches of the suitable intermediate or the final active substance.

Changes to manufacturing processes

When changes are proposed to a manufacturing process in which it has been demonstrated initially that a class 1 or class 2 solvent is below the defined threshold for routine testing, the manufacturer should consider the impact of manufacturing process changes on solvent levels and revalidate as necessary.

Annex II: residues of solvents used in the manufacture of finished products

Justification for the use of organic solvents in the manufacture of finished products

Organic solvents can be used in the manufacture of medicinal products for different reasons.

For example:

- as a granulation solvent for the manufacture of tablets;
- as part of a tablet coating solution;
- as a solvent for adhesives used in manufacture of transdermal patches;
- as a solvent for polymers used in manufacture of implants.

The justification and choice of solvents used in the manufacture of finished products should be included within the pharmaceutical development documentation. For example, ethanol can be proposed as a solvent for the granulation and/or for the coating solution if the drug substance is demonstrated to be very sensitive to moisture. Organic solvents seem to be unavoidable when certain polymers have to be introduced into the product manufacture. The use of a class 1 solvent in the manufacture of the finished product is not considered acceptable.

Specifications for finished products when organic solvents have been used in their manufacture

A test for organic residues of solvents that are used in the manufacture of finished products should be included in the product specifications. Process validation results are not considered to adequately justify the omission of such a test from the specifications, but they can be used to justify skip testing.

If class 3 solvents only are used, routine testing by loss on drying with a < 0.5% acceptance limit is acceptable when this test is appropriately validated for determination of the relevant solvent(s). Where residues of class 3 solvents cannot be reduced to this level and/or where class 2 solvents are used in the production, specific (chromatographic) techniques should be used.