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

Annexes to:

EMA/CHMP/ICH/82260/2006 - ICH Q3C Guideline on impurities: guideline for residual solvents

EMA/CVMP/VICH/502/1999 - VICH GL18 Impurities: residual solvents in new veterinary medicinal products, active substances and excipients

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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1. Introduction

The two (V)ICH residual solvents guidelines, ICH Q3C Impurities: Guideline for residual solvents (EMA/CHMP/ICH/82260/2006) and VICH GL18 Guideline on impurities: residual solvents in new veterinary medicinal products, active substances and excipients (EMA/CVMP/VICH/502/1999), have been in operation 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.

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

2.1. *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 in Table 1, unless otherwise justified*".

The justification for using a class 1 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 class 1 solvent benzene is unavoidable in a specific chemical reaction such as a Friedel-Crafts reaction, or the desired purity profile can only be obtained by using a given class 1 solvent. If a class 1 solvent is involved in a very early step of the manufacturing process and the absence of this solvent is shown in a suitable intermediate, such an approach may be acceptable.

The maximum acceptable limit for a class 1 solvent in the final active substance, whether it is used as a raw material (solvent or reagent), a starting material, generated as a by-product, or present as an impurity in another solvent, should always comply with the limits prescribed in the relevant aforementioned ICH/VICH guideline on impurities: residual solvents, if tested.

2.1.1. Class 1 solvents intentionally used or generated in the manufacturing process (A)

Certain class 1 solvents, such as benzene and 1,2-dichloroethane, can be used in the synthesis of starting materials and, exceptionally, active substances. Benzene can also be generated as a by-product from a chemical reaction (for example, Grignard reaction, when phenylmagnesium halide used in excess is hydrolysed to yield benzene).

Indeed, the use of class 1 solvent is unavoidable when it is a structural part of the active substance.

Benzene, for example, is commonly used in the very early steps of syntheses, well before the starting material is 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). However, if a class 1 solvent is used or generated after introduction of the starting materials, a justification demonstrating that its use is unavoidable, should be provided.

In case a class 1 solvent is used or generated prior to the *last step of the manufacturing process*[1], it should be routinely controlled, either in the concerned starting materials, a suitable intermediate or in the final active substance. One of the following scenarios should be considered.

- When a class 1 solvent is controlled in the concerned starting material or in a suitable intermediate with a limit not exceeding the corresponding (V)ICH limit, it is considered possible to not include additional control of this solvent in the active substance specification if after the control point, downstream in the manufacturing process, the use, generation or introduction as impurity (see section 2.1.2) of the respective class 1 solvent is excluded.
- When a class 1 solvent is controlled in the concerned starting material or in a suitable intermediate with a limit above the corresponding (V)ICH limit, it is considered possible to not include control of this solvent in the active substance specification if it can be demonstrated that the level of class 1 solvent in the final active substance will not exceed 30% of the corresponding (V)ICH limit. The proposed control limit should be established in line with actual levels of the class 1 solvent present in the corresponding starting material or intermediate.
- Should a class 1 solvent not be controlled at the starting material or intermediate stage, routine control of this solvent should be included in the active substance specification. However, it is considered possible to apply skip testing if the level of the solvent does not exceed 30% of the corresponding (V)ICH limit in the active substance. Data should be provided from at least 6 consecutive pilot scale batches or 3 consecutive production scale batches of the active substance.

If the use or generation of a class 1 solvent in the last step of the manufacturing process is unavoidable, routine test in the active substance specification with a limit not exceeding the corresponding (V)ICH limit is expected.

See also decision tree A.

2.1.2. Class 1 solvents present as an impurity in another solvent (B)

A class 1 solvent in an active substance may arise from another solvent (the originator solvent), for example, toluene or acetone where benzene is a known process impurity.

In case a risk for the presence of a class 1 solvent as an impurity in another solvent is identified, it should be controlled, either in the corresponding originator solvent(s), a suitable intermediate or in the final active substance.

Where a class 1 solvent might be present as an impurity in a solvent used anywhere in the manufacturing process after introduction of starting materials, one of the following scenarios should be considered.

- When a class 1 solvent is controlled in the originator solvent(s) or in a suitable intermediate with a limit not exceeding the corresponding (V)ICH limit, no further control in the active substance specification is needed if the prerequisites mentioned in the first bullet point of section A are met
- When a class 1 solvent is controlled in the originator solvent(s) or in a suitable intermediate

[1] i.e. last process step involving the use of a solvent, irrespective of the associated unit-operation, e.g. chemical reaction or purification step

with a limit above the corresponding (V)ICH limit, it needs to be unambiguously demonstrated by analysis results that the presence of this solvent does not exceed 30% of the corresponding (V)ICH limit in the active substance, in order to avoid additional testing in the final active substance. The proposed control limit should be established in line with actual levels of the class 1 solvent present in the corresponding originator solvent or intermediate. A limit above the corresponding (V)ICH limit could also be acceptable if based on spike and purge data under the process relevant conditions.
Alternatively, a scientific risk assessment based on physicochemical properties (e.g., volatility) and any process steps designed to remove class 1 solvent could be acceptable (on a case-by-case basis).

- Should a class 1 solvent not be controlled in the originator solvent(s) or at the intermediate stage, control of this solvent should be included in the active substance specification, with a possibility to apply skip testing, if the level of the solvent does not exceed 30% of the corresponding (V)ICH limit in the active substance.

2.1.3. Considerations for omission of any testing (C)

Class 1 solvents used, generated or present as impurity in a process solvent prior to the last step of the manufacturing process do not need to be listed on any specification if the process chemistry is understood and process parameters that impact levels of class 1 solvents are included in the control strategy, resulting in consistent removal below 10% of the corresponding (V)ICH limit in the active substance. Data should be presented, along with an appropriate justification for applying this strategy. Test results from a minimum of 6 pilot scale batches or 3 production scale batches may be sufficient.

For class 1 solvents used, generated or present as impurity in a process solvent in the last step of the manufacturing process, the omission of any control is not acceptable and a strategy as described under sections 2.1.1 or 2.1.2 should be implemented.

2.2. *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 manufacturing process 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.

2.2.1. Class 2 solvents used prior to the last step of the manufacturing process

Class 2 solvents used prior to the last step in the manufacturing process do not have to be included in the active 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 omission of a 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 production scale batches of the suitable intermediate or the final active substance.

2.2.2. Class 2 solvents used in the last step of the manufacturing process

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

2.3. *Changes* to manufacturing processes

If suppliers or specifications of solvents are changed or when other changes are proposed to a manufacturing process, the manufacturer should consider the impact of the changes on class 1 and/or class 2 solvent levels. As necessary, the manufacturer should revalidate compliance and reconsider the applied control strategy.

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

3.1. *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 active 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.

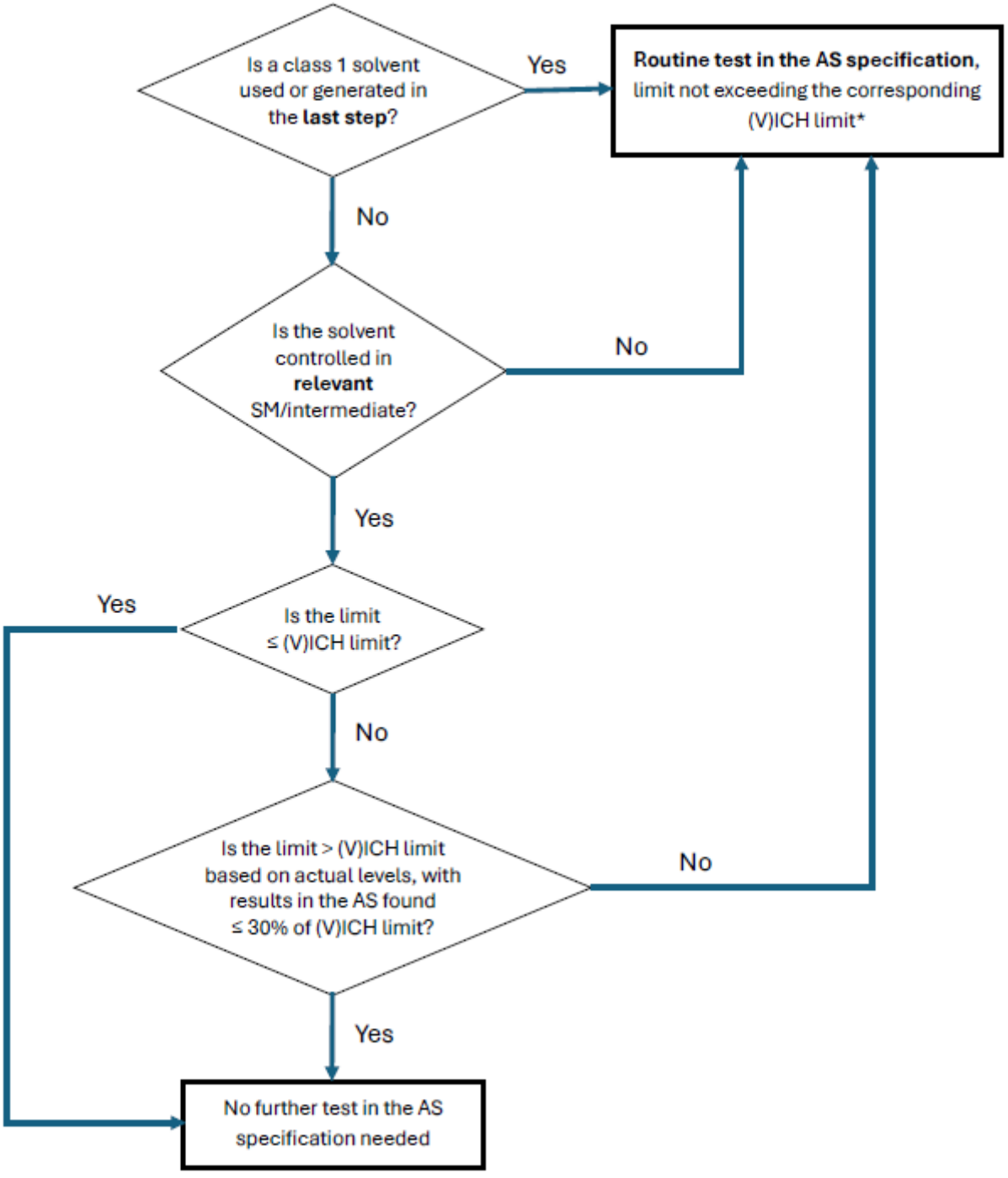
3.2. *Specifications for* finished products when organic solvents have been used in their manufacture

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.

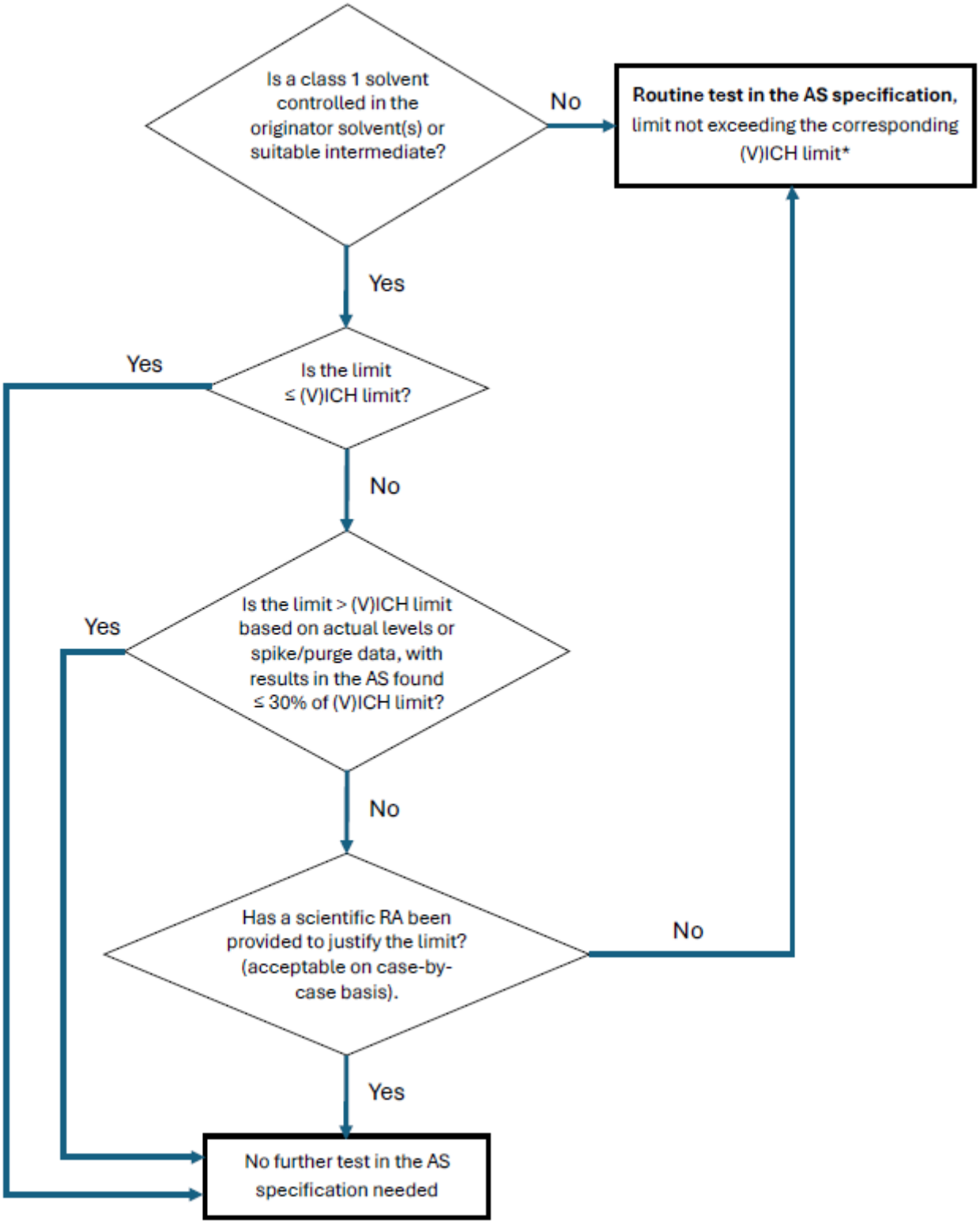
Appendix: Decision trees for Specifications for class 1 residual solvents in active substances

A. Class 1 solvents intentionally used or generated in the manufacturing process



* For possibility of applying skip testing, see the Annex I text Section 2.1.1.

B. Class 1 solvents present as an impurity in another solvent



* For possibility of applying skip testing, see the Annex I text Section 2.1.2.

C. Considerations for omission of any testing