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Guideline on Setting Specifications for Related Impurities in Antibiotics

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Executive summary

Antibiotics active substances currently on the market are produced by chemical synthesis, fermentation or fermentation followed by one or more synthetic steps (semi-synthetic substances). Fermentation processes are, in comparison to synthetic processes, more variable and less controllable, so the impurity profile of an active substance whose manufacturing process involve fermentation may be more complex and less predictable than that of a purely synthetic product. For these reasons fermentation products and semi-synthetic substances are not included in the scope of the ICH Q3 and the VICH 10/11 guidelines, that set thresholds for identification, reporting and qualification of related impurities in active substances manufactured by chemical synthesis.

This guideline has been developed in order to provide guidance on how specifications for related impurities in antibiotics that are fermentation products or semi-synthetic substances derived from fermentation products, therefore not included in the scope of the (V)ICH guidelines mentioned above, should be set.

Thresholds are given in the guideline for reporting, identification and qualification of related impurities for antibiotics medicinal products whose active substance is produced by fermentation or semi-synthesis. For cases where the active substance consists of a mixture of closely related compounds, where it may be difficult to apply general thresholds, general guidance is given on how to set specific thresholds and specifications and how to qualify impurity profiles. The relationships between the requirements in the guideline and the Ph.Eur. applicable chapters and monographs are also addressed.

1. Introduction (background)

Most of the antibiotics currently on the market are produced by chemical synthesis or fermentation. In certain cases the chemical structure of the antibiotics obtained by fermentation is further modified by some synthetic steps, before the substance is used as an active substance in the manufacture of medicinal products (semi-synthetic substances).

Fermentation processes involve biological systems which are less predictable, less controllable and more complex than straightforward chemical reactions. Because of this, the variability in products derived by fermentation is often greater then in products derived by chemical synthesis. Thus, the impurity profile of a fermentation product may be more complex and less predictable than that of a synthetic product.

For these reasons, fermentation products and semi-synthetic substances derived from them are not included in the scope of the ICH Q3 and the VICH 10/11 guidelines that set thresholds for identification, reporting and qualification of related impurities in active substances manufactured by chemical synthesis. These thresholds are defined in the guidelines as limits above which an impurity has to be either identified reported or qualified, and the same limits are applied in the Ph.Eur. general monograph ‘Substances for pharmaceutical use’. Fermentation products and their semi synthetic derivatives are also excluded from the scope of this general monograph.

In the absence of other guidance, related impurities in these products have been assessed on a case-by-case basis, which has resulted in the acceptance of different impurity thresholds for the same antibiotic and for different compounds within the same class (e.g. cephalosporins). There is also a need to ensure that the authorisation of new antibiotics is enabled by consistent approaches in setting limits for their impurities.

It is therefore necessary to provide guidance, based on current practice and experience, to formulate general recommendations for impurity thresholds in antibiotics produced through fermentation. These are presented in this guideline.

Even so, it is acknowledged that in some cases higher thresholds may be acceptable if necessary and justified taking account of use and exposure of the drug substance/product.

2. Scope

This document provides guidance for marketing authorisation applications on setting specifications for related impurities in antibiotics (i.e. antibacterial substances) that are fermentation products or semi-synthetic substances derived from fermentation products. It is foreseen to widen the scope to other antibiotics (e.g. antifungal substances) at a later stage. It provides guidance for the content and qualification of related impurities in active substances and medicinal products. The guideline is not intended to apply to new active substances used in investigational medicinal products used in clinical trials.

In this guideline thresholds are given for reporting, identification and qualification of related impurities. For antibiotics where the active substance consists of a mixture of closely related compounds where it may be difficult to apply these general thresholds, general guidance is given on how to set thresholds and specifications and how to qualify impurity profiles. The thresholds given in this guideline would represent a general set of requirements, and this could be subject, for specific substances or products, to adaptation to the specific situation. Further requirements might be introduced when considered necessary, e.g. for safety reasons.

This guideline does not cover residues from the fermentation process, i.e. residues from the producer micro-organism, culture media, substrates and precursors. This is covered in the Ph.Eur. general monograph 'Products of fermentation'. (This monograph applies to substances manufactured by fermentation, and not to substances manufactured by semi-synthesis).

This guideline applies for new applications for marketing authorisation and for new manufacturer variations. The guideline will not be applied retrospectively, but it is intended that this guideline will act as a stimulus to establish best practice and to initiate the revision of relevant Ph.Eur. monographs. For new applications this guideline should be read in conjunction with any existing Ph.Eur. monograph for the active substance.

3. Legal basis

This guideline has to be read in conjunction with the introduction and general principles (4) and part 1 of the Annex I to Directive 2001/82 and 2001/83 as amended.

4. General requirements

The impurity profile depends very much on the manufacturing process; even for the same strain of a micro-organism, impurity profiles may be different. In general, purification steps including column chromatography and ultra-filtration steps may be crucial to achieve a sufficiently pure active substance.

Semi-synthetic substances are not within the scope of the Ph.Eur. general monograph 'Products of fermentation'. However, the specification of the fermented starting material should be justified with reference to current guidance, including general concepts described in this general monograph, if necessary.

The shorter the synthetic route after the fermentation and the more complex the fermented starting material, the more relevance the general monograph has. Therefore, a detailed description of the fermentation steps as well as other aspects addressed in the general monograph, in particular purification steps, should be presented for semi-synthetic antibiotics, unless justified by the non-complexity of the fermented starting material and the number and/or nature of the synthetic steps following fermentation.

These synthetic steps should contribute to a relevant depletion and inactivation of fermentation by-products in the final active substance, so e.g. esterification, etherification and salification of fermentation products (e.g. Erythromycin derivatives like Erythromycin ethylsuccinate or Erythromycin lactobionate) are not considered as significant synthetic steps which would justify an omission of a detailed description of the fermentation process, in particular of the purification.

In cases where the fermented starting material is not complex and taking into consideration the number and nature of the synthetic steps after fermentation, it may be sufficient to have a suitable specification for the fermented starting material including assay, component distribution (if relevant) and related impurities (specified, unspecified, and total). This should be in any case justified.

Related impurities observed after fermentation include by-products, intermediates and degradation products. For semi-synthesis the impurities also include the fermented starting material and related substances in this starting material, synthesis by-products (including those derived from impurities in the starting material), synthesis intermediates and degradation products.

Specifications should be given for critical intermediates. These specifications should include limits for specified and single unknown impurities. The applicant should provide a discussion on potential impurities, how they are removed and which impurities appear in the active substance.

Even if manufactured by fermentation or semi-synthesis, an antibiotic may be structurally well defined, and thus it may be efficiently purified. For active substances manufactured by semi-synthesis, the quality of the fermented starting material may be important.

For antibiotics manufactured by fermentation, the active substance may consist of a mixture of closely related compounds that show the relevant biological activity. In such cases it may be difficult to decide whether a compound is part of the active substance or should be regarded as an impurity when setting specifications (e.g. gentamicin). The definition of which substances are components of the active substance should be based on pre-clinical and clinical studies unless the active substance is described in a Ph.Eur. monograph where the active substance components are defined. Related compounds that are not defined to be components of the active substance are regarded as related impurities.

The thresholds given in the ICH Q3 and VICH GL 10/11 guidelines and in the guideline 'Chemistry of New Active Substances' (CPMP/QWP/130/96 Rev 1, EMEA/CVMP/541/03) do not apply to fermentation products and semi-synthetic substances derived form fermentation products. For other aspects, where specific guidance is not given in the present guideline, reference is made to the principles described in these guidelines.

5. Impurity profiling and reporting, identification and qualification thresholds

For antibiotic drug substances, the impurity profile should be characterised according to the guidance described in ICH 3QA (VICH GL10).

In accordance with that guidance, with respect to related substances, limits should be set for:

- Each specified identified impurity

- Each specified unidentified impurity
- Any unspecified impurity, with an acceptance criterion of not more than the identification threshold
- Total impurities.

Exceptionally, if it is shown that it is not practically possible to identify an individual impurity, then as a minimum, sufficient evidence of its structure should be provided to show that it may be satisfactorily classified as a related substance of the parent compound. In this case, it should be specified using an appropriate analytical marker e.g. HPLC Relative Retention Time, as a specified unidentified impurity.

In case of a very complex impurity profile or where two impurities are very similar, it may not be technically feasible to obtain peak separation. In such cases it may be necessary to set a limit for a combination of unresolved peaks. In this case, where possible, thresholds should be applied for the combination of peaks. For qualification, the composition of the batches used in the toxicological studies should be taken into account.

As a general principle, for impurities which are not structurally closely related (see section 5.3 below) to the parent compound, thresholds as given by ICH Q3A (VICH GL10) should be applied unless stated differently in the following sections.

For the reasons discussed in section 4 above and taking into account that the duration of treatment with antibiotics is in most cases limited, for antibiotic related substances the thresholds to be applied are higher than those stated in Q3A/GL10, and also different for each of the different classes of antibiotic. These thresholds are given below.

5.1. Active substances manufactured by semi-synthesis

Semi-synthetic substances are obtained from a fermented starting material by a process involving at least cleavage and formation of covalent bonds followed by extraction/purification steps. Acceptance criteria for related impurities should be set in accordance with the thresholds given below.

The Q3A thresholds for reporting, identification and qualification apply. For active substances used in veterinary medicine only the VICH GL 10 thresholds for reporting, identification and qualification (of 0.10%, 0.20% and 0.50%, respectively) apply.

If the semi-synthetic active substance consists of a family of closely related compounds it may be necessary to apply requirements up to the thresholds described for substances manufactured by fermentation, family of compounds (see 5.3). A justification should be given.

5.2. Active substances manufactured by fermentation, single compound

Acceptance criteria for related impurities should be set in accordance with the thresholds given below.

Reporting threshold: 0.10%
Identification threshold: 0.15%
Qualification threshold: 0.15%

For active substances used in veterinary medicine only the VICH GL 10 thresholds for reporting, identification and qualification (of 0.10%, 0.20% and 0.50%, respectively) apply.

5.3. Active substances manufactured by fermentation, family of compounds

Acceptance criteria for related impurities should be set in accordance with the thresholds given below.

Reporting threshold: 0.10%
Identification threshold: 0.15%
Qualification threshold: 0.50%/0.15%

For active substances used in veterinary medicine only, the following thresholds apply:
Reporting threshold: 0.10%
Identification threshold: 0.20%
Qualification threshold: 0.50%

The qualification threshold of 0.50% for structurally closely related compounds is combined with a qualification threshold of 0.15% for other related compounds. Justification for claiming that a related impurity (compound not defined to be included in the active substance) is structurally closely related to the parent compounds should at least be based on evidence such as HPLC/mass spectrometry or HPLC/diode-array detection or the use of reference materials. The proposed 0.50%/0.15% limits are suggested to apply even for daily doses of ≥2 g, which may be relevant for some of these antibiotics.

For each class of antibiotic, it is better and may be easier, to optimise purification steps, in order to decrease the level of impurity to below the qualification threshold, than providing safety data.

It is also acknowledged for known active substances that comparative impurity profiles with innovator material may be supportive in the characterisation of impurity profiles.

6. New applications and variations

6.1. New active substances

The impurity profile should be characterised and individual impurities should be identified and, if necessary, qualified by an appropriate battery of non-clinical and clinical tests.

6.2. Known active substances, not subject to a Ph.Eur. monograph

The impurity profile should be characterised and individual impurities should be identified and, if necessary, qualified by an appropriate battery of non-clinical tests and other suitable means, including reference to already approved material.

6.3. Active substances subject to a Ph.Eur. monograph

6.3.1. Known active substances subject to a Ph.Eur. monograph with transparency statement and the means of their identification[1]

The impurity profile should be characterised and individual impurities identified.

Known impurities should be controlled according to the monograph requirements.

New impurities should be identified, when necessary to comply with this guideline.

[1] Some monographs include a section, "Identification of impurities", where relative retention with reference to the main peak is described for the principal impurity peaks. In some cases the use of Ph.Eur. CRS is described.

New impurities should be qualified when necessary to comply with this guideline by the appropriate battery of non-clinical tests or other suitable means.

6.3.2. Known active substances subject to Ph.Eur. monograph, with transparency statement, but no means of their identification

The impurity profile should be characterised and individual impurities identified, when necessary to comply with this guideline, using as reference the transparency statement of the monograph.

Known impurities should be controlled according to the monograph requirements.

Any new impurities should be identified and qualified, when necessary to comply with this guideline, by the appropriate battery of non-clinical tests or by other appropriate means, including reference to innovator material.

6.3.3. Known active substances subject to Ph.Eur. monograph, without transparency statement

The impurity profile should be characterised and individual impurities identified, when necessary to comply with this guideline.

Impurities should be qualified, when necessary to comply with this guideline, by the appropriate battery of non-clinical tests and by other means, including reference to innovator material.

6.3.4. Revision of monographs

A revision of the monograph should be initiated when:

- The means of identification of known impurities have been established
- New impurities have been identified or qualified.

7. Specifications for medicinal products

Specifications should be set for related impurities that are degradation products. Impurities originating from the manufacture of the drug substance should not be specified unless they are also degradation products.

Information on the impurity profile may be obtained from the source of the active substance.

Acceptance criteria for related impurities should be set within the thresholds given below. The same specifications should apply to the product after any opening/reconstitution/dilution (in-use shelf life) as for the finished product, unless justified by suitable qualification data e.g. by comparison to levels found in the original product.

Active substance manufactured by semi-synthesis:

Reporting threshold: 0.1%
Identification and qualification thresholds: 0.2%

Active substance manufactured by fermentation, single compound:

Reporting threshold: 0.15%
Identification threshold: 0.2%
Qualification threshold: 0.2%

Active substance manufactured by fermentation, family of compounds:

Reporting threshold: 0.15%
Identification threshold: 0.2%
Qualification threshold: 0.5%/0.2%

For all three groups of active substances, higher acceptance criteria for identification and qualification may be set according to the doses/thresholds in ICH Q3B for low doses.

For veterinary medicinal products the VICH GL 11 thresholds for reporting, identification and qualification (0.3%, 1.0% and 1.0%, respectively) should be applied.

8. Analytical procedures

When analysing the final active substance and the medicinal product, whenever possible, an external standard should be used calculating w/w to evaluate and exclude any possible mass imbalance. If using area normalisation the relevant components and related impurities should give similar responses in the detector. Otherwise response factors should be used.

Area normalisation may be acceptable for certain active substances consisting of a family of compounds. In area normalisation the area percentage is calculated on the basis of the total area in the chromatogram, instead of using an external standard. This may be used when analysing relevant intermediates. When using area normalisation linearity for the intended range should be demonstrated and an unambiguously defined disregard criterion should be given.

When performing qualification of an impurity profile versus the innovator product, a sufficiently specific analytical procedure should be used. For complicated mixtures the separation technique (e.g. HPLC) should be combined with mass spectrometry (or diode-array detection, where justified). For routine testing simpler procedures may be used, if justified.

The quantitation limit for the analytical procedure should be not more than (≤) the reporting threshold. For substances having weak chromophores, this will in some cases lead to high reporting thresholds.

Definitions

Fermented active substances: Primary or secondary metabolites of micro-organisms such as bacteria, yeast, fungi and micro-algae, irrespective of whether or not the micro-organism have been modified by traditional procedures or by recombinant DNA technology.

References

1. 'Impurities in new drug substances (revised)' (CPMP/ICH/2737/99) (ICH Q3A(R))
2. 'Impurities in new drug products' (CPMP/ICH2738/99) (ICH Q3B(R))
3. 'Control of impurities of pharmacopoeial substances' (CPMP/QWP/1529/04 and EMEA/CVMP/059/04-FINAL)

4. 'Specifications: test Procedures and acceptance criteria for new drug substances and new drug products: chemical substances' (CPMP/ICH/367/96) (ICH Q6A)
5. 'Assessment of the quality of medicinal products containing existing/known active substances' (EMEA/CHMP/CVMP/QWP/296289/2008)
6. 'Impurities in new veterinary drug substances' (EMEA/CVMP/VICH/837/99-Rev.1) (VICH 10(R))
7. 'Impurities in new veterinary medicinal products' (EMEA/CVMP/VICH/838/99-Rev.1) (VICH 11(R)
8. 'Test procedures and acceptance criteria for new veterinary drug substances and new medicinal products: chemical substances' (EMEA/CVMP/VICH/810/04-corrigendum) (VICH 39)
9. 'Chemistry of New Active Substances' (CPMP/QWP/130/96 Rev 1)
10. 'New impurities control: setting specifications for antibiotics and synthetic peptides: proceedings from EDQM symposium, Strasbourg 21-22 September 2006'
11. European Pharmacopoeia general monograph 'Substances for Pharmaceutical Use'
12. European Pharmacopoeia general chapter 5.10 'Control of impurities in substances for pharmaceutical use'
13. European Pharmacopoeia general monograph 'Products of fermentation'

Annex: explanatory note regarding thresholds

In setting up the thresholds, the antibiotics have been classified regarding the method for their preparation (whether they are prepared by fermentation only or the fermentation is followed by synthetic steps) and their composition (whether the antibiotic is a single substance or a mixture of closely related compounds). Thus, the differences in thresholds for reporting, identification and qualification between these different classes of antibiotics are mainly for technical/practical reasons.

As a background for the proposed thresholds current practice for Ph.Eur. monographs and assessment practice in connection with the issuing of CEPs has been considered.

Active substances manufactured by semi-synthesis:

Purification steps and the subsequent synthetic steps make it possible to obtain active substances with low levels of impurities. In many cases, the" starting material" for the synthetic steps is a well characterised compound of good purity (e.g. 6-APA and 7-ACA), similar to starting materials manufactured by synthesis. Therefore ICH thresholds are proposed.

Active substances manufactured by fermentation, single compound:

Consisting of only one active compound these substances are relatively easy to purify, and as a consequence of this it is possible to set relatively low thresholds.

Active substances manufactured by fermentation, family of compounds:

When the active substance is a mixture of closely related compounds it is difficult to purify this mixture from other closely related compounds present (and excessive purification could also lead to a different component distribution). Some of these other components have the same antibiotic activity as the components defined to be included in the active substance, while other components do not have the same activity. These components are handled as related impurities, but due to the complex situation it is difficult to set very low thresholds. It is proposed to have a relatively low qualification threshold, and

to include the possibility of having a wider qualification threshold for structurally closely related substances (based on evidence such as HPLC/mass spectrometry).