



COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)
COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

**CONCEPT PAPER ON THE DEVELOPMENT OF A GUIDELINE ON SETTING
SPECIFICATIONS FOR RELATED IMPURITIES IN ANTIBIOTICS**

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1. INTRODUCTION

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 products and semi-synthetic substances derived from them are not included in the scope of the ICH Q3A(R) and the VICH 10 (R) guidelines that set thresholds for identification, reporting and qualification of related impurities. 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.

2. PROBLEM STATEMENT

The (V)ICH guidelines and the Ph.Eur. general monograph mentioned above provide guidance to industry on how to set specifications for related impurities, and to assessors on how to assess related impurities, in medicinal products containing as active substance antibiotics produced by chemical synthesis, in particular by specifying the acceptable thresholds for identification, reporting and qualification of impurities mentioned above.

On the other hand, for fermentation products and semi synthetic substances, which are excluded from the scope of both guidelines and the general monograph, no general acceptance criteria have been established for related impurities, and currently related impurities are assessed on a case-by-case basis. This is particularly critical taking into account that fermentation products and their semi synthetic derivatives often present an impurity profile which is more complex than the impurity profile of purely synthetic substances.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

The concepts of identification, reporting and qualification thresholds, already established for substances manufactured by chemical synthesis, are also valid for antibiotics produced by fermentation and antibiotics whose production involves synthetic steps after fermentation. For these products, the active substance may consist of a mixture of closely related compounds that show the relevant biological activity, so it can be difficult to decide, when setting specifications, for substances which are closely related, if they belong to the active substance or should be considered as related impurities.

Also, it might be difficult to develop a proper analytical procedure for the assay, with the required specificity and sensitivity, which applies to all the closely related substances forming the active substance but does not apply to any of the related impurities.

In some cases the thresholds applicable to products obtained by chemical synthesis may be also applicable to certain classes of antibiotics where a series of synthetic and purification steps are performed after fermentation (e.g. cephalosporins). This was questioned by experts from industry at a recent symposium (see list of references), who stated that some of the Ph.Eur. monographs for cephalosporins are outdated, for example with specifications for any other impurity not in line with the guidelines and the Ph.Eur. general monograph 'substances for pharmaceutical use' (e.g. 1.0%). In such situations, different regulatory authorities within Europe are applying different quality standards to the same pharmacopoeial materials. Some regulators may even request compliance with the (V)ICH thresholds for unspecified impurities.

This shows that currently there is no harmonised approach for setting specifications for related impurities in antibiotics prepared by fermentation and semi-synthetic processes.

4. RECOMMENDATION

For the active substances under consideration, a harmonised approach for setting and assessing specifications for related impurities is desirable. This harmonised approach may also be reflected later on in pharmacopoeial monographs. So, there is a need to develop guidance for both applicants and assessors on how to set specifications and assess related impurities in antibiotics other than those manufactured by chemical synthesis.

It is also recommended that the guideline address a general approach on how to apply principles similar to those given in the ICH Q3 and VICH 10/11 guidelines, as regards impurity control. In particular, guidance regarding qualification of impurity profiles and principles for setting thresholds and specifications in active substances and in finished products should be developed.

The guideline should take into account the specificities of different classes of compounds, as there might be specific aspects for specific classes of compounds to be considered, and it might be not possible to develop general concepts applicable to all the various classes of antibiotics whose production involves fermentation, so grouping of substances according to the main chemical structures (e.g. penicillins, tetracyclines etc.) might be considered..

Also, special consideration should be given to the differences in the manufacturing process for the different classes of products e.g. purely fermentation products, semi-synthetic products involving few synthetic steps after fermentation and semi-synthetic products involving major modifications by chemical synthesis after fermentation.

It should be made clear that the provisions in the guideline would represent a general set of minimum requirements, and that this could be subject, for specific products, to adaptation to the specific situation, and further requirements might be introduced when considered necessary e.g. for safety reasons.

It is further recommended that the requirements in the guideline would be reviewed at some stage in the light of experience gained during assessment, in order to further harmonise practices between Member States.

5. TIMETABLE

It is anticipated that a draft guideline, to be published for 6 months external consultation, will be available within 10 months after adoption of the Concept Paper. The finalised guideline is expected to be published within 6 months after the end of the external consultation period.

6. RESOURCE REQUIREMENTS FOR PREPARATION

The development of the guideline will be carried out by QWP.

QWP will appoint a rapporteur among its members who will:

- Prepare the draft guideline
- Review internal comments before the guideline is published for external consultation
- Prepare a new draft for publication
- Review the external comments received after the expiration of the external consultation period is expired
- Prepare the overview of comments
- Prepare a new draft for finalisation.

The guideline will be discussed at several times as necessary at QWP meetings (expected 3/4 times) and at QWP/Interested Parties meetings.

A specific drafting group with the participation of the rapporteur and other QWP experts might be set up if considered necessary by QWP (expected 1-2 1 day meetings with the participation of 4-5 experts).

The preparation of this guideline will involve cooperation with the EDQM, the Safety Working Parties (human and vet) and the Biologics Working Party.

7. IMPACT ASSESSMENT (ANTICIPATED)

The guideline will clarify requirements for regulators and industry (applicants for marketing authorisation and manufacturers of drug substances) as regards how to set specifications for related impurities in antibiotics whose manufacturing process involves fermentation. Assessment practices in this context will be harmonised.

The assessment times should be reduced as a result of the publication of the guideline, and the number of questions in the list of questions of marketing authorisation applications in the mutual recognition, decentralised and centralised procedures should be reduced as well.

The development of the guideline will provide general agreed principles to be applied when setting specifications for related impurities for the products in question. These principles will facilitate the revision of existing monographs and the development of new monographs of the European Pharmacopoeia, thus providing the bases for further harmonisation.

8. INTERESTED PARTIES

Member States National Competent Authorities, EDQM, CHMP, CVMP, the Safety Working Parties (human and vet) and the Biologics Working Party are the main regulatory interested parties.

Pharmaceutical industry associations e.g. EFPIA, EGA, IFAH, APIC-CEFIC, AEGSP are the main external interested parties.

9. REFERENCES TO LITERATURE, GUIDELINES ETC

'Impurities in new drug substances (revised)', (CPMP/ICH/2737/99) (ICH Q3A(R))

'Impurities in new drug products', (CPMP/ICH2738/99) (ICH Q3B(R))

'Control of impurities of pharmacopoeial substances', (CPMP/QWP/1529/04 and EMEA/CVMP/059/04-FINAL)

'Specifications: test Procedures and acceptance criteria for new drug substances and new drug products: chemical substances', (CPMP/ICH/367/96) (ICH Q6A)

'Impurities in new veterinary drug substances', (EMEA/CVMP/VICH/837/99-Rev.1) (VICH 10(R))

'Impurities in new veterinary medicinal products', (EMEA/CVMP/VICH/838/99-Rev.1) (VICH 11(R))

'Test procedures and acceptance criteria for new veterinary drug substances and new medicinal products: chemical substances', (EMEA/CVMP/VICH/810/04-corrigendum) (VICH 39)

'New impurities control: setting specifications for antibiotics and synthetic peptides, proceedings from EDQM symposium, Strasbourg 21-22 September 2006'

European Pharmacopoeia general monograph 'Substances for Pharmaceutical Use', proposal for revision, Pharmeuropa Vol 19 No 3, July 2007

European Pharmacopoeia general chapter 5.10 'Control of impurities in substances for pharmaceutical use'