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GUIDELINE ON SUMMARY OF REQUIREMENTS FOR ACTIVE SUBSTANCES IN THE QUALITY PART OF THE DOSSIER

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SUMMARY OF REQUIREMENTS FOR ACTIVE SUBSTANCES IN THE QUALITY PART OF THE DOSSIER

The legal basis for this Guideline is:

- Directive 2001/82/EC and 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for veterinary and human use, respectively.
- Commission Directive 2003/63/EC of 25 June 2003, amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use.

This Guideline is intended to provide guidance regarding the requirements to be included for chemical and herbal active substances in the quality part of the dossier, depending on the described classification.

Biological active substances and immunological active substances, as defined in Annex I of the Directive 2001/82/EC and Directive 2001/83/EC, as amended, are excluded from the scope of this Guideline.

1. CLASSIFICATION OF ACTIVE SUBSTANCES

Active substances can be classified into:

- new active substances, used for the first time in a medicinal product either for human or veterinary use
- existing active substances not described in the European Pharmacopoeia (Ph.Eur.) or the pharmacopoeia of an EU Member State
- existing active substances described in the Ph.Eur. or in the pharmacopoeia of an EU Member State

Active substances can further be divided into:

- inorganic substances
- herbal drugs and herbal drug preparations
- organic substances (isolated from material of animal or human origin)
- organic substances (synthetic or semi-synthetic or isolated from herbal sources or micro-organisms)

2. FEASIBLE WAYS TO SUBMIT THE REQUIRED INFORMATION

Depending on the kind and classification of the active substance, the required data may generally be submitted in one of the following three ways – see sections 2.1, 2.2 and 2.3.

For new active substances option 2.2 or 2.3 would apply. For existing substances option 2.1 (where applicable) has the advantage of generally avoiding any subsequent reassessment. Options 2.2 or 2.3 are also applicable.

Option 2.4 may be in addition to option 2.2 and option 2.3 and can only be considered as a specific option in very exceptional cases.

2.1 Certificate of Suitability to the Monograph of the European Pharmacopoeia (CEP)

The active substance manufacturer should submit documentation to the European Pharmacopoeia Secretariat with a view to evaluating the suitability of the pharmacopoeial monograph in relation to the manufacturing method actually used, cf. Appendix I of the Council of Europe Resolution AP-CSP (99) 4 *Certification of Suitability to the Monographs of the European Pharmacopoeia.*

The Applicant should include a copy of the most current CEP in the dossier, together with a written assurance that no significant changes in the manufacturing method have taken place following the granting of the certificate or its last revision.

Along with the CEP, the Applicant should supply results of batch analysis demonstrating compliance with the Ph.Eur. monograph and including any additional tests/limits listed on the CEP (e.g. residual solvents, additional impurity tests).

In the case of sterile substances, the Applicant should make sure that a full of the sterilisation process as specified on the CEP as well as results of any tests applied (in particular the test of the monograph) and validation data are provided in the application file.

The CEP may not necessarily address all relevant parameters and in these cases the Applicant should supply additional data, e.g. stability data to support a retest period (only if retest date not mentioned on the CEP), physico-chemical characteristics such as particle size and polymorphism.

2.2 Active Substance Master File (ASMF) Procedure

Full details of chemistry, manufacturing process, quality controls during manufacture and process validation for the active substance may be submitted in a Active Substance Master File as outlined in the Guideline *Active Substance Master File Procedure EMEA/CVMP/134/02 or CPMP/QWP/227/02).* In such cases, The Applicant's Part needs to be included in the marketing authorisation (MA) application.

Proof of structure may not be necessary where this can be shown by specific identification tests in relation to reference substances sufficiently described in the dossier.

In the case of *pharmacopoeial active substances:*

- Stability data may not be necessary where adequate literature evidence can be cited and summarised and where the monograph covers the degradation products for which suitable limits have been set as indicated in the Note for Guidance *Stability testing on Existing Active Substances and Related Finished Products (EMEA/CVMP/846/99 or CPMP/QWP/122/02).*
  In this situation the Applicant should demonstrate that the substance complies with the monograph immediately before use.

- Special emphasis should be given to demonstrating that those potential impurities, most likely to arise during synthesis, from the actual manufacturing process can be controlled by the manufacturer, particularly where these differ from any included in the monograph. In case that not all potential impurities are mentioned in an impurity section of the monograph, the Applicant should demonstrate whether the tests of the monograph can control these additional impurities. If the manufacturer uses different methods to control specified impurities, equivalence to the pharmacopoeial method should be demonstrated. The toxicological implications of impurities not included by the monograph should be

addressed. That means that the specificity of the method to these additional impurities must always be investigated, but the discussion of the toxicological implications (qualification) is only required if defined thresholds are exceeded, cf. Note for Guidance *Impurities in New Veterinary Drug Substances (CVMP/VICH/837/99),* Note for Guidance *Impurities in New Drug Substances (CPMP/ICH/2737/99) or* Ph.Eur. *General Monographs: Substances for Pharmaceutical Use*.

2.3 Full details of manufacture

The Applicant may submit as part of the MA application full details of chemistry, manufacturing process, quality controls during manufacture and process validation for the active substance as outlined in the Note for Guidance *Chemistry of Active Substances (3AQ5a)* or Note for Guidance *the Chemistry of New Active Substance (CPMP/QWP/130/96).*

Proof of structure may not be necessary where this can be shown by specific identification tests in relation to reference substances sufficiently described in the dossier.

In the case of *pharmacopoeial active substances:*

- Stability data may not be necessary where adequate literature evidence can be cited and summarised and where the monograph covers the degradation products for which suitable limits have been set as indicated in the Note for Guidance *Stability testing on Existing Active Substances and Related Finished Products (EMEA/CVMP/846/99 or CPMP/QWP/122/02).*
  In this situation the Applicant should demonstrate that the substance complies with the monograph immediately before use.

- Special emphasis should be given to demonstrating that those potential impurities, most likely to arise during synthesis, from the actual manufacturing process can be controlled by the manufacturer, particularly where these differ from any included in the monograph. In case that not all potential impurities are mentioned in an impurity section of the monograph, the Applicant should demonstrate whether the tests of the monograph can control these additional impurities. If the manufacturer uses different methods to control specified impurities, equivalence to the pharmacopoeial method should be demonstrated. The toxicological implications of impurities not included by the monograph should be addressed. That means that the specificity of the method to these additional impurities must always be investigated, but the discussion of the toxicological implications (qualification) is only required if defined thresholds are exceeded, cf. Note for Guidance *Impurities in New Veterinary Drug Substances (CVMP/VICH/837/99),* Note for Guidance *Impurities in New Drug Substances (CPMP/ICH/2737/99) or* Ph.Eur. *General Monographs: Substances for Pharmaceutical Use*.

2.4 Other supportive data in consideration of the qualification of impurities

With respect to the ASMF Procedure (2.2) or full information as part of the MA application (2.3), the Applicant may supply other supportive data obtained from the active substance manufacturer, in order to consider impurities as qualified. This may include the following:

a) information as to the length of time that the active substance from the particular named source has been on sale in the European Union and elsewhere, including the types of dosage forms (and the target species) involved;

b) a statement that, in the above period, there had been no significant change in the method of manufacture leading to a change in the impurity profile of the active substance;

c) if possible, evidence that samples of the active substance from the named source had been supplied to the Ph.Eur. Commission or a national Pharmacopoeia Commission and have been taken into account in the development of the monograph.

In very exceptional cases, option 2.4 may be a possible approach to providing reassurance to the authorities of the suitability of an official pharmacopoeial monograph (Ph.Eur or the pharmacopoeia of an EU Member State) to control a very well-defined and well-established active substance from an innovator with long and safe patient exposure from the named source.

3. NEW ACTIVE SUBSTANCES

For new chemical active substances, the requirements are set out in the Note for Guidance *Chemistry of Active Substances (3AQ5a)* or Note for Guidance *Chemistry of the New Active Substance (CPMP/QWP/130/96).*

For new herbal drugs/herbal drug preparations the requirements are set out in the Note for Guidance *Quality of Herbal Medicinal Products (CPMP/QWP/2819/00; EMEA/CVMP/814/00).*

In all cases the possible content of any residual solvents should be discussed and where appropriate limits for such solvents should be given in accordance with the Guideline *Impurities: Residual Solvents (CVMP/VICH/502/99 or CPMP/ICH/283/95)* or the Ph.Eur. *General Texts: Residual Solvents*. Batch analysis should be provided.

The stability data to be presented are described in the Guidelines *Stability testing of new drug substances and products (CPMP/ICH/2736/99), Stability testing of new veterinary drug substances and medicinal products (CVMP/VICH/889/99), Photostability testing of new drug substances and medicinal products (CPMP/ICH/279/95) and Photostability testing of new veterinary drug substances and medicnal products (CVMP/VICH/901/00)*.

In cases where biological substances are used during manufacture (e.g. during the fermentation process), the viral safety of the substances should be appropriately demonstrated, and where applicable compliance with the Note for Guidance *Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products* should be demonstrated.

The information may be supplied either as part of the MA application or using the ASMF Procedure.

4. EXISTING ACTIVE SUBSTANCES NOT DESCRIBED IN THE EUROPEAN PHARMACOPOEIA OR A PHARMACOPOEIA OF AN EU MEMBER STATE

In principle, the requirements are as set out above for new active substances. Full information should be submitted. However, information from literature may be permitted (e.g. to consider impurities as qualified).

In all cases the possible content of any residual solvents should be discussed and where appropriate, limits for such solvents should be given in accordance with the Guideline *Impurities: Residual Solvents (CVMP/VICH/502/99 or CPMP/ICH/283/95)* or the Ph.Eur. *General Texts: Residual Solvents*. Batch analysis should be provided.

Where appropriate, evidence of proof of structure may be omitted (e.g. where this can be carried out by specific identification tests in relation to a reference substance, sufficiently described in the dossier, or where reference is made to the pharmacopoeia of a third country).

In cases where an active substances is described neither in the European Pharmacopoeia nor in the pharmacopoeia of a Member States, compliance with the monograph of a third country pharmacopoeia can be accepted. In such cases, the Applicant shall submit a copy of the monograph accompanied where necessary by the validation of the test procedures contained in the monograph and by translation where appropriate, cf. *Annex I (part 2.C, section 1.1, last paragraph) of Directive 2001/82/EC or Annex I (section 3.2, sixth paragraph) of Directive 2001/83/EC (as amended by the Commission Directive 2003/63/EC).*

In relation to purity testing the suitability of the monograph to control those potential impurities, most likely to arise during synthesis, should be demonstrated along the same lines as for substances of the Ph.Eur. or the pharmacopoeia of an EU Member State.

For active substances not described in an official pharmacopoeial monograph (Ph.Eur or the pharmacopoeia of an EU Member State) stability studies are always required, cf. Note for Guidance *Stability Testing of Existing Active Substances and Related Finished Products (EMEA/CVMP/846/99 or CPMP/QWP/122/02).*

In cases where biological substances are used during manufacture (e.g. during the fermentation process), the viral safety of the substance should be appropriately demonstrated, and where applicable compliance with the Note for Guidance *Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products* should be demonstrated.

The information may be supplied either as part of the MA application or using the ASMF Procedure.

5. EXISTING ACTIVE SUBSTANCES DESCRIBED IN THE EUROPEAN PHARMACOPOEIA OR THE PHARMACOPOEIA OF AN EU MEMBER STATE

Each batch of these substances must comply with the current requirements of the Ph.Eur. or the pharmacopoeia of an EU Member State.

In each case evidence should be presented to demonstrate the suitability of the pharmacopoeial monograph to adequately assess the quality of the material from the named manufacturer. The general Ph.Eur. monograph on *Substances for Pharmaceutical Use* has to be applied together with the relevant Ph.Eur. monograph.

In all cases the possible content of any residual solvents should be discussed and, where appropriate, limits for such solvents should be given in accordance with the Guideline *Impurities: Residual Solvents (CVMP/VICH/502/99 or CPMP/ICH/283/95)* or the Ph.Eur. *General Texts: Residual Solvents*. Batch analysis should be provided.

Evidence of the stability of the active substance may be provided from the literature in those cases where the monograph covers the degradation products including suitable limits, cf. Note for Guidance *Stability Testing of Existing Active Substances and Related Finished Products (EMEA/CVMP/846/99 or CPMP/QWP/122/02).* In this case the Applicant should demonstrate

that the substance complies with the monograph immediately before use.

In cases where it is necessary for the particular intended use to control the bulk substance with respect to solid-state properties (e.g. particle size, polymorphism), suitable acceptance criteria additional to the official pharmacopoeial monograph must be proposed with details of test methods, validation data (where relevant), and batch analyses.

5.1 Inorganic substances

In the case of inorganic substances, it should be stated whether the manufacturer has used a process which may leave impurities that are not adequately controlled by the monograph and, in such case, details of the tests (incl. validation data, where relevant) additional to those of the pharmacopoeial monograph should be supplied.

The information may be supplied preferably in the form of a CEP, or as part of the MA application or using the ASMF Procedure.

5.2 Herbal drugs and herbal drug preparations

For herbal drugs/herbal drug preparations the requirements are set out in the Note for Guidance *Quality of Herbal Medicinal Products (CPMP/QWP/2819/00; EMEA/CVMP/814/00).*

In particular, it should be stated whether the cultivator/manufacturer has used a method of cultivation and preparation liable to leave impurities not adequately controlled in the monograph (e.g. pesticides residues, fumigants, mycotoxins). In that case, details of the tests (including validation data, where relevant) additional to those of the pharmacopoeial monograph should be supplied.

The information may be supplied either in the form of a CEP, or as part of the MA application or using the ASMF Procedure.

5.3 Organic substances (isolated from material of animal or human origin)

In the case of organic substances extracted from material of human or animal origin, full information should be supplied and in particular, the collection, treatment and storage of the animal or human source material, isolation of the active substance, specification and control methods for source materials, measures to ensure freedom from potentially pathogenic agents (e.g. viruses, prions) and stability should be provided.

The information may be supplied preferably in the form of a CEP (not applicable for substances obtained from human tissues), or as part of the MA application, or using the ASMF Procedure.

5.4 Organic substances (synthetic or semi-synthetic or isolated from herbal sources or from micro-organisms)

In relation to such organic active substances from any manufacturer, there may be impurities present which are not adequately controlled by the official pharmacopoeial monograph. The suitability of the pharmacopoeial monograph and any additional method to test for those impurities, most likely to arise during synthesis, should, in all cases, be demonstrated.

In cases where biological substances are used during manufacture (e.g. during the fermentation process), the viral safety of the substance should be appropriately demonstrated, and where applicable compliance with the Note for Guidance *Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal*

products should be demonstrated.

In the case of substances isolated from herbal sources, the potential for impurities arising from cultivation and/or preparation (eg. pesticide residues, fumigants, mycotoxins) should be addressed.

The information may be supplied either in the form of a CEP, or as part of the MA application or using the ASMF Procedure.

ANNEX-GLOSSARY

Acceptance Criteria
Numerical limits, ranges, or other suitable measures for acceptance of test results of analytical procedures.

Active substance
Any substance or mixture of substances intended to be used in the manufacture of the a medicinal product and that, when used in the production of a drug, becomes an active ingredient of the medicinal product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Degradation product
A molecule resulting from a chemical change in the active substance brought about over time and/or by the action of, e.g., light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system. Also called decomposition product.

Fermentation products
Active or inactive pharmaceutical substances produced by controlled fermentation as indirect gene products. The are primary or secondary metabolites of micro-organisms such as bacteria, yeasts, fungi or micro-algae, whether or not modified by traditional procedures or recombinant DNA (rDNA) technology.

Herbal drugs
Mainly whole, fragmented or cut, plants, parts of plants, algae, fungi, lichen in an unprocessed state, usually in dried form but sometimes fresh.

Herbal drug preparations
Preparations obtained by subjecting herbal drug to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation.

Impurity
Any component present in the active substance that is not the chemical entity defined as the active substance.

Impurity profile
A description of the identified and unidentified impurities present in an active substance.

Qualification
The process of acquiring and evaluating which establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

Reference substance
A substance of established quality and purity, used as a reference standard for routine laboratory analysis.

Re-test period
The period of time during which the active substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given medicinal product, provided that the active substance has been stored under defined conditions. After this period, a batch of active substance destined for use in the manufacture of a medicinal product, should be re-tested for compliance with the specification and then used immediately. A batch of active substance can be re-tested multiple times and a different portion of the batch used after each re-test, as long as it continues to comply with the specification.

Specification
A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which an active substances or medicinal product should conform to be considered acceptable for its intended use.

Validation
A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria.