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(CVMP)

GUIDELINE ON

THE CHEMISTRY OF NEW ACTIVE SUBSTANCES

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GUIDELINE ON THE CHEMISTRY OF NEW ACTIVE SUBSTANCES

Guideline concerning the application of Directive 2001/82/EEC with a view to the granting of a marketing authorisation for a new medicinal product.

INTRODUCTION

This guideline has been prepared in parallel to the Human Guideline on the Chemistry of New Active Substances (CPMP/QWP/130/96, Rev.1) (revised in accordance with the new structure of the quality part of dossiers for human medicinal products, format ICH-CTD), as identical information is required for new active substances used in either human or veterinary medicinal products. Nonetheless, all relevant information stated in this Guideline should be included in Part IIC1 and Part IIF1 of the dossier in accordance with the Notice to Applicants format for veterinary medicinal products. For convenience, the correlation table between the quality part of the EU-CTD and the NTA (veterinary) format is attached in Annex I.

Scope of the Guideline

The purpose of this Guideline is to set out the type of information required for the control of new active substances (new chemical entities) used for the first time in a veterinary medicinal product[1)]. This guideline is applicable for (semi-)synthetic active substances; it is not applicable for biologicals, biotechnological products, radiopharmaceuticals and radiolabelled products.

ASMF

As an acceptable alternative to submission of detailed active substance information in the Marketing Application, the Active Substance Master File (ASMF) procedure may be used. For ASMF Procedures and requirements, please *see reference 4* in the Appendix to this Guideline.

BODY OF DATA

1 GENERAL INFORMATION

This section deals with the identity, nomenclature and chemical structure of the active substance which is the subject of the application for marketing authorisation. Only brief information of physical characteristics should be listed, as full details and proof of structure are required in a separate section (see section 3.1).

1.1 Nomenclature

Information on the nomenclature of the active substance should be provided, if relevant:

- Recommended International Nonproprietary Name (rINN);
- Compendial (e.g. European Pharmacopoeia) name;
- National Approved Names: BAN, DCF, DCIT, JAN, USAN, Company or Laboratory Code;
- Systematic Chemical Name(s) (IUPAC nomenclature);
- Other Names (e.g. proprietary);
- Other non-proprietary name(s);
- Chemical Abstracts Service Registry Number (CASRN);
- Chemical Abstracts Index Name.

[1)] *For those active substances which are new to veterinary medicine but are used in human medicine and are described in the European Pharmacopoeia the information may also be supplied in the form of a Certificate of suitability to the monograph of the European Pharmacopoeia (CEP).*

1.2 Structure

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass (Mr) should be provided. Along with the stoichiometric formula and relative molecular mass Mr, the structural formula should display the stereochemistry (indicated conventionally) of the active substance. If this information is not available a detailed description of the nature of the substance should be given. If appropriate, the Mr of the therapeutically active moiety should also be included.

1.3 General Properties

The appearance of the material is to be described briefly. A list of physicochemical and other relevant properties of the active substance should be provided, in particular physico-chemical properties that affect pharmacological efficacy and toxicological safety such as solubilities, pKa, polymorphism, isomerism, log P, permeability, etc.

See reference 8

2 MANUFACTURE

2.1 Manufacturer(s)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

2.2 Description of Manufacturing Process and Process Controls

The description of the active substance manufacturing process represents the applicant's commitment for the manufacture of the active substance. Information should be provided to adequately describe the manufacturing process, including special unit operations and process controls. Any steps of the process that may have an impact on the quality of the active substance or intermediates and which are classified as 'critical', should be identified and described in detail (see also under section 2.4).

Flow diagram of the manufacturing process

A flow diagram of the synthetic process(es) should be provided that includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and active substance reflecting stereochemistry, and identifies operating conditions, unit operations, catalysts and solvents.

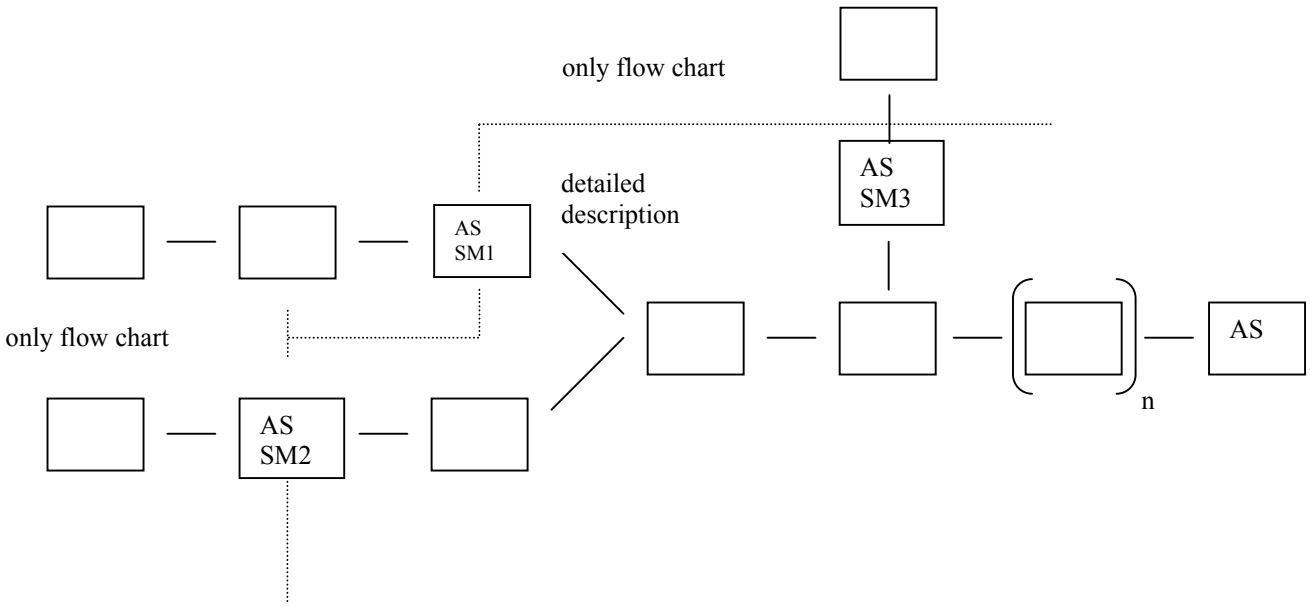
Active Substance (AS) starting material

Generally, the description of the process and the synthesis schematic should include all the steps of the process, proceeding from the starting material(s) to the isolated intermediates, and ultimately to the active substance. Use of starting materials marks the beginning of the detailed description of the process.

Starting materials should be fully characterized to ascertain suitability for intended use, and the possibility of transferring impurities from the starting material to the final active substance should be discussed. Relevant viral safety and/or TSE data must be provided if any animal-derived material is used during the active substance manufacturing process (e.g. arising from fermentation, enzymes, amino acids, etc). Starting materials from vegetable origin should be fully characterized to ascertain suitability, and a contaminant profile should be established and submitted.

The applicant should propose and justify which substance should be considered as the AS starting material (SM), e.g. incorporated as a significant structural fragment into the structure of the active substance. The name and address of the starting material supplier(s) should be provided. Indications on the synthetic process under form of a flow-chart may be useful to evaluate the suitability of its specification(s).

Schematic description (illustrative only):



If the description of the route of synthesis consists of only one step and the starting material is a substance described in the European Pharmacopoeia, the substance should either have a certificate of the Ph.Eur. (CEP), or the proof of conformity should be provided (*see reference 11*). Alternatively, such a starting material may already be authorized as an active substance in a marketing authorisation.

Generally the full description of the process should cover all the synthetic steps critical for the safety (impurities) and the efficacy (structural part responsible for the activity) of the active substance.

Sequential procedural narrative

A sequential procedural narrative of the manufacturing process should be submitted. This narrative should include the quantities (or ranges) of raw materials, starting materials and intermediates, solvents, catalysts and reagents used in manufacture of a representative-scale commercial batch. The narrative should describe each step in the manufacturing process, and identify critical steps, process controls employed, and ranges for equipment operating conditions (e.g. temperature, pressure, pH, time, flow-rate, etc).

The control of critical steps and intermediates have to be described in section 2.4.

Scale of Manufacture, Range, Yield

The description of the process should indicate the scale of manufacture and the range for which the considered process may be used. It may be helpful to indicate the yield or yield range produced at each stage.

Alternative processes

Alternative processes should be explained and described with the same level of detail as the primary process. The process description should fully define the method of synthesis. However, if alternative steps or solvents are proposed they should be justified providing sufficient evidence that the final quality of the material (i.e. active substance or isolated intermediate) obtained remains unchanged. If differences in impurity profiles are encountered they should be analyzed with validated methods and shown to be toxicologically acceptable.

Reprocessing

The cases when reprocessing is carried out should be identified and justified. Any data to support this justification should be either referenced or filed in section 2.5. The reprocessing method should be clearly described.

2.3 Control of Materials

Materials used in the manufacture of the active substance (e.g., raw materials, starting materials, isolated intermediates, solvents, reagents, catalysts, process aids, etc) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials meet standards appropriate for their intended use should be provided. If quality of a specific input material is critical for the quality of the active substance, and non-compendial test methods are used to control that material, suitable validation data for control tests carried out should be submitted.

Biologically-sourced materials

Information on the source, processing, characterization and control of all materials of biological origin must be provided, including viral and/or TSE safety data.

Active Substance-starting material

For AS starting materials, as defined in section 2.2, complete specifications should be provided, including an impurities profile. Impurities present in a starting material may be carried through the synthesis/process unchanged or as derivatives, and should therefore be controlled in the starting material by appropriate acceptance criteria with suitably validated methods. Acceptance criteria should be established by the applicant based on evaluation of the fate of impurities present in the starting material, when subjected to the normal synthesis/process.

Solvents and processing aids used in the final step

Specifications for solvents used in synthesis and for process-aids (e.g. activated charcoal used for absorbing impurities, and diatomaceous earth used to aid filtration) should be submitted. Solvents used at the final stages of the synthesis require greater control (i.e. tighter specifications) than solvents used in earlier stages.

See reference 7

Acceptance criteria

The criteria for accepting or rejecting batches of the above-mentioned materials should be indicated. The control of starting materials should be designed to detect isomeric (if relevant) or other impurities which are potentially reactive and could be carried through to the final product of the synthesis.

See reference 1, 2, 3 and 8

2.4 Controls of Critical Steps and Intermediates

Critical Steps

Tests and acceptance criteria (with justification based on experimental data) performed at critical steps identified in section 2.2 of the manufacturing process should be provided. A critical step is defined as one where the process conditions, test requirements or other relevant parameters must be controlled within predetermined limits to ensure that the AS meets its specification.

Critical steps could be for instance:

- Mixing of multiple components
- Phase change and phase separation steps
- Steps where control of temperature and pH are critical.
- Intermediate steps which introduce an essential molecular structural element or result in a major chemical transformation
- Intermediate steps which introduce (or remove) significant impurities to (or from) the active substance
- Final purification step

Steps which have an impact on solid-state properties and homogeneity of the active substance, are always considered as critical, particularly if the active substance is used within a solid dosage form, since they may adversely effect dissolution of the active substance from the dosage form and thereby impact bioavailability.

Intermediates

Information on the quality and control of intermediates isolated during the process should be provided. For key intermediates which are those which influence final quality of the active substance, the analytical methods used to control them should be suitably validated if they are not compendial ones.

Some impurities may be formed or eliminated during the process, for which suitable in-process controls should be carried out with justified ranges and documented.

See reference 8

2.5 Process Validation and/or Evaluation

Steps that are identified in section 2.4 as critical for the quality of the active substance should be validated.

Process validation and/or evaluation studies for aseptic processing and sterilisation should be provided.

2.6 Manufacturing Process Development

A description and discussion should be provided of any significant changes made to the manufacturing process and/or manufacturing site of the active substance used in producing non-clinical, clinical, scale-up, pilot, and, if available, production scale batches.

Reference should be made to the active substance data provided in section 4.4.

See reference 6

3 CHARACTERISATION

3.1 Elucidation of Structure and other Characteristics

Evidence of chemical structure

Confirmation of structure based on e.g., synthetic route and spectral analyses, information regarding the potential for isomerism, identification of stereochemistry, or potential for forming polymorphs should be included.

This section should include the research and development program performed to verify the structure and the chemical and physico-chemical properties of the new active substance. The results described in this section should be reflected in the control tests on the active substance to check batch-to-batch uniformity. A scientific discussion of the chemistry of the active substance should be provided, including unequivocal proof of structure, configuration, conformation (if relevant) and potential isomerism. This should include a presentation of the stereochemical properties of the molecule e.g. geometric isomerism (cis/trans, E/Z), number of chiral centres and configuration at each centre (*see reference 3*). It is important that the evidence of structure should be related to the actual material to be used in the marketed product, especially for highly complex molecular structures.

If the data included in this section originates from a synthetic process other than the one covered by the application (i.e. different routes), evidence may be required to confirm the structural identity of the materials from a different origin. This is particularly important where toxicological studies have been carried out on material from a different origin.

Publication references may be included if the synthetic route and structure of the intermediates are cited as structural evidence.

The information will normally include such evidence as:

- Elemental analysis with theoretical values
- Infra-red spectra with interpretation
- Nuclear magnetic resonance spectra with interpretation
- Discussion on UV characteristics including pH dependent shifts
- Mass spectrum with interpretation and discussion of results
- Discussion of the synthetic route as evidence of structure
- Evidence of structure of key intermediates of synthesis (e.g. using IR, NMR, etc.)
- Characteristic chemical reactions which are diagnostic of the structure of the molecule
- X-ray crystallography with interpretation and discussion of results (refer to section 2.3)
- Optical rotation (absence of optical rotation should be reported if it serves to demonstrate the racemic nature of an asymmetric molecule)
- Evidence of the indicated relative molecular mass

The relevance of the eventual or possible isomers regarding activity should be discussed (*see reference 3*).

Physico-chemical Characteristics

Information set out under the relevant headings below should cover aspects of physicochemical characteristics which have been investigated, whether or not they are included in the monograph for the active substance.

Polymorphism

Polymorphism is the property of a chemical substance to exist in different crystalline forms. Some active substances exist in different solid state forms (polymorphs or solvates) possessing different physico-chemical properties. These forms may affect processability, stability, dissolution and bioavailability of the drug product.
Examples of procedures commonly used to determine the existence of multiple forms are:

- Melting point (including hot-stage microscopy)
- Solid state IR and NIRS
- X-ray powder diffraction
- Thermal analysis procedures (like DSC, TGA and DTA)
- Raman spectroscopy
- Scanning electron microscopy
- Solid state NMR

The presence of polymorphic forms and solvates and the methods of detection and control should be discussed, or their absence demonstrated.

See reference 8

Solubility

Numeric solubility values (e.g. mg/ml) for the active substance in water at various temperatures should be provided, as well as the corresponding pH values for the equilibrium solubility-test solutions. Data for solubility in other solvents may also be provided. The test procedures used for solubilities should be described.

Physical characteristics

Physical properties should be stated here and if significant, information on particle size (complete particle size profile), solvation, melting point, boiling point should be added.

pKa and pH values

The pKa values of the active substance and the pH in solutions of defined concentration should be stated. In the case of a salt, the corresponding values of the base or acid should be stated.

Other characteristics

Information is to be provided concerning the following:

- Physico-chemical characteristics (e.g., oil/water partition coefficient, octanol/water partition coefficient, log P, etc)
- Physical properties of significance should be stated

3.2 Impurities

Information on impurities should be provided. The related substances considered as potential impurities arising from the synthesis should be discussed and described briefly together with an indication of their origin. In each case, it should be stated whether actual samples of such impurities have been synthesized for test purposes, structural analysis data and which of the analytical methods described have been used to detect that impurity. Possible routes of degradation should also be discussed (see section 7.1). The analytical methods (with limits of detection (LOD) and limits of quantitation (LOQ)) used to detect each of the likely impurities considered above or other related impurities, the exact identities of which may be unknown, should be described. Copies of relevant chromatograms should be provided. A summary should be given on the nature and levels of the actual impurities detected in the batch samples of the material. Justification should be provided for selecting the limits based on safety and toxicity data, as well as on the methods used for the control of impurities (see section 4.4.).

See references 3, 5, 6, 7, 8, 9 and 10

4 CONTROL OF THE ACTIVE SUBSTANCE

4.1 Specification

The active substance specification should be provided.

The following tests should be performed as a minimum required and appropriate acceptance criteria applied:

- Description
- Identification
- Impurities
- Assay and/or potency

Additional tests may be required depending on the nature of the active substance.

See references 6 and 8

4.2 Analytical Procedures

Details of the analytical procedures used for testing the active substance should be provided. They should be described in such a way that they can be repeated by an Official Medicines Control Laboratory.

See reference 1

Analytical Development

Any critical aspects of significance concerning analytical development in regard to the active substance specification should be mentioned. The discussion here should highlight any unusual aspects concerning the tests dealing with the specification of the active substance. Tests for purity and impurity levels can be discussed under the section on impurities. If biological control procedures are necessary, then particular emphasis should be laid on the discussion of the test precision and accuracy.

4.3 Validation of Analytical Procedures

Analytical validation data, including experimental results for the analytical procedures used for the control of the active substance, should be provided. Validation of analytical tests concerning the active substance should be performed according to the requirements of the current Guidelines (*see references 1 and 2*).

4.4 Batch Analyses

Description of batches and results of batch analyses should be provided.

- Batches or material used in the pre-clinical tests and clinical studies reported in support of the application.
- Data illustrating the actual results obtained from routine quality control of the active substance. Recent consecutive batches (at least 3) which are representative (not –less than 10% of maximum commercial batch size at the time of the approval) of the active substance which will be supplied for the purpose covered by the marketing authorization to show that the proposed methods will give routine production material which falls within the specification limits cited. Information on production size batches should be provided, if necessary on an on-going basis, after approval.

The results should include:

- Date of manufacture
- Batch size and number
- Place of manufacture (data from all manufacturing sites must be provided)
- Results of analytical determination
- Use of batches

Test results should be expressed numerically e.g. impurity levels. Results which merely state that the material “complies” with the test are insufficient, especially if a relatively wide limit is allowed in the specification. The batch analyses should include all the tests in the specification. There may, however, be cases where previous batches were tested using a slightly different specification. In these cases, a brief explanatory note should be included. Any apparently inconsistent or anomalous results in the batch analyses should be explained.

See references 6, 7 and 8

4.5 Justification of Specification

Justification for the active substance specification should be provided. The specification should be based on results from preclinical, clinical and production scale batches and taking into account the qualification of impurities.

See references 6, 7 and 8

5 REFERENCE STANDARDS OR MATERIALS

Information on the reference standards or reference materials used for testing of the active substance should be provided: specifications, full analytical and physico-chemical characterizations, impurities profile, etc. The criteria for establishing the reference substances (primary and secondary) for routine analysis should be given with full analytical profiles.

See references 3 and 8

6 CONTAINER CLOSURE SYSTEM

A brief description of the bulk storage container-closure system(s), including specifications and details of the materials of construction should be provided. If the bulk storage container-closure system is critical for protecting and assuring the quality of the active substance, the choice of the container primary packaging material (e.g. polyethylene bag) and secondary packaging (e.g. fibre or metal drum) should be justified.

7 STABILITY

7.1 Stability Summary and Conclusions

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions (light stress, higher temperature, etc), as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

See references 5, 9 and 10

7.2 Post-approval Stability Protocol and Stability Commitment

A post-approval stability protocol and stability commitment should be provided.

See references 5, 9 and 10

7.3 Stability Data

Detailed results of the stability studies (e.g. forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included. The major degradation pathways of the active substance, the storage conditions and the retest period should be defined.

See references 1, 2, 5, 9 and 10

References

1 Guideline on Validation of Analytical Procedures: Definition and Terminology CVMP/VICH/590/98.
2 Guideline on Validation of Analytical Procedures: Methodology CVMP/VICH/591/98.
3 Note for Guidance on Investigation of Chiral Active Substances EMEA/CVMP/128/95.
4 Guideline on Active Substance Master File procedure EMEA/CVMP/134/02.
5 Guideline on Stability testing: Photostability testing of new veterinary drug substances and medicinal products CVMP/VICH/901/00.
6 Guideline on Impurities in New Veterinary Drug Substances CVMP/VICH/837/99.
7 Guideline on Impurities: Residual solvents CVMP/VICH/502/99.
8 Note for Guidance on Specifications: Test procedures and acceptance criteria for new veterinary drug substances and medicinal products: Chemical substances CVMP/VICH/xxx/yy *(in progress).*
9 Note for Guidance on Stability testing of New Veterinary Drug Substances and Medicinal ProductsCVMP/VICH/899/99.
10 Note for Guidance on Stability testing of existing active substances and related finished products EMEA/CVMP/846/99.
11 Note for Guidance on Summary of requirements for active substances in the quality part of the dossier EMEA/CVMP//1069/02.

ANNEX I

Correlation table between EU-CTD and NTA
http://pharmacos.eudra.org/F2/eudralex/vol-2/B/ctd2003july.pdf

pages 17-19.