CHEMISTRY OF ACTIVE SUBSTANCES

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Additional Notes	**This note for guidance concerns the application of Part 2, section C of the Annex to Directive 75/318/EEC as amended with a view to the granting of a marketing authorisation for a medicinal product. The section on impurities is replaced by the guideline *Impurities in New Active Substances* for new active substances. For abridged applications, biotechnological/biological products and other products exempted from the "impurities" guideline, these requirements continue to apply.**

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CHEMISTRY OF ACTIVE SUBSTANCES

1. INTRODUCTION

The purpose of this note for guidance is to set out the type of information required for the control of new active substances used for the first time in a medicinal product, which are not described in the European Pharmacopoeia or a pharmacopoeia of a Member State.

2. IDENTITY OF MATERIAL

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 details of physical characteristics should be stated, as full details and proof of structure are required later.

2.1 Nomenclature

– International Non-Proprietary Name (INN),

– National Approved Names, ( )

– US Adopted Name (USAN),

– Laboratory Code(s),

– Systematic Chemical Name(s),

– Other Names (e.g. Proprietary).

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2.2 Description

– physical form,

– structural formula,

– molecular formula,

– relative molecular mass.

A brief description should be given of the appearance of the material. Where possible, the structural formula should be given diagrammatically with all known stereochemistry indicated conventionally, with molecular formula and relative molecular mass; otherwise a detailed description of the nature of the substance should be given.

The relative molecular mass of the therapeutically active moiety should also be included, where appropriate.

3. MANUFACTURE

A concise but comprehensive account of the manufacture of the active substance should be provided. The headings given below should be followed where the active substance concerned is a totally synthetic product. Some modification may be required where the molecule is only partially synthetic e.g. penicillin-derivatives.

3.1 Manufacturing process

When a complete or partial chemical synthesis is involved, this should be represented by diagrams of the chemical reactions in the form of a flow sheet.

3.2 Description of process

An appropriate description should be given of each stage of the manufacture, including, where applicable:

– solvents and reagents used,

– catalysts used,

– conditions of reactions where these are critical,

– information on intermediates which are isolated and purified,

– details of the final purification and solvents involved.

The description of the process should indicate the scale of manufacture. It is often helpful if an indication of the yield produced at each stage is given.

The description must normally fully define the method of synthesis. However, if alternative steps or solvents are proposed these should be justified and show that the final quality of material obtained does not differ significantly.

3.3 Quality control during synthesis

3.3.1 Starting materials

Describe the analytical controls which are applied to ensure that the starting materials, which make a significant contribution to the molecular formula, and any reagents are correctly identified and are shown to be of a satisfactory quality. An indication of the content of significant impurities in starting materials should be given. Specifications for solvents used in the final stages of synthesis, crystallisation and/or washing should be submitted.

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

3.3.2 Intermediate control

The quality control checks which are carried out at each stage of the process and on the isolated intermediates should be described. A statement of the test procedure(s) and criteria for acceptance should be given for each stage, where appropriate.

4. DEVELOPMENT CHEMISTRY

This section should indicate the research and development programme which has been undertaken on the new active substances to investigate the evidence of structure and the chemical and physico-chemical properties.

The findings described in this section should be reflected in the control tests on the active substance by which batch-to-batch uniformity is controlled.

4.1 Evidence of chemical structure

A scientific discussion of the chemistry of the active substances molecule should be given and should include, where applicable, unequivocal proof of structure, configuration, conformation and potential isomerism. This should include a presentation of the stereo chemical properties of the molecule, e.g. geometric isomerism (cis/trans, E/Z), number of chiral centres and configuration at each centre. A summary and discussion of the unequivocal proof of structure by the experts involved in the Expert Report can often provide useful additional background information. Care should be taken that the visual evidence of spectra is completely legible when reproduced in the copies of the application. 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. Where the data included in this sub-heading are from a source of synthetic process other than that covered by the application (i.e. different routes),evidence may be required to confirm the structural identity of the different materials. This is particularly important where toxicity work has been carried out on material from a different source (see also item 7). Where the synthetic route and structure of the intermediates are cited as evidence of structure, references to relevant published papers in the literature would be helpful. Where relevant, the information might include such evidence as:

– elemental analysis with theoretical values,

– infra-red spectra with interpretation,

– nuclear magnetic resonance spectra with interpretation including C13 data where relevant,

– 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 4.2.3),

– optical rotation with discussion of optical purity in the case of isomerism. (Absence of optical rotation should be reported when this serves to illustrate that an asymmetric molecule is racemic),

– evidence of the indicated relative molecular mass.

The relevance of the isomer to activity should be discussed.

4.2 Physico-chemical characteristics

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

4.2.1 Solubility

The solubility in water, including pH dependence, and in other solvents should be given as numerical values with particular reference to the formulation and test procedures.

4.2.2 Physical characteristics

An indication should be given as to whether the substance is crystalline, amorphous, etc. and where relevant, information on particle size, solvation, melting point, boiling point etc.

4.2.3 Polymorphism

Where relevant, the presence of polymorphic forms and the methods of detection and control should be discussed, or their absence confirmed.

4.2.4 pKa and pH values

Where relevant, the pKa values of the active substance and the pH in solutions of defined concentration should be given. In the case of a salt, this information for the corresponding base or acid should be given.

4.2.5 Other characteristics

Any other relevant information should be given (for oil/water partition coefficient, numerical values should be presented).

4.3 Analytical development

Any critical aspects of analytical development relevant to the active substance monograph should be mentioned. The discussion here should highlight any unusual aspects of the tests for identity, physico-chemical characteristics and content which are used in the monograph. (Tests for purity and freedom from contamination can be discussed under the section on impurities). Discussion of the precision and accuracy of test procedures is particularly applicable to substances where biological control is necessary.

5. IMPURITIES

A broad outline should be given of the research programme which has been undertaken to demonstrate that the test procedures used for impurity control in the active substance specification are valid including limit of detection and limit of quantification. Negative information can sometimes be important.

5.1 Impurities

– by-products of the synthesis arising from side reactions, impurities in the starting materials or isomerisation,

– residual solvents and reagents,

– trace elements arising from the use of catalysts or from other sources,

– degradation products (see note for guidance *Stability Tests on Active Substances and Finished Products*).

A list and brief description of the products which have been considered as potential impurities arising from the synthesis should be given. In each case, it should be stated whether actual samples of such impurities have been synthesised for test purposes and which of the analytical methods described under 5.2 have been used to detect those impurities.

Possible routes of degradation should also be discussed on the basis of results of investigations on exposure of the substances to stress conditions (such as heat, light, pH, moisture and other relevant factors).

5.2 Test procedures

The analytical methods with limits of detection of the test procedures which have been used to detect each of the likely impurities considered in 5.1 above or other related impurities, the exact identities of which may be unknown, should be described. Copies of relevant chromatograms should be provided.

5.3 Summary of results

A summary should be given of the nature and levels of impurities which have been detected in the batch samples of the material. The Expert Report should provide a justification for selecting the limits (based on findings from toxicity testing) and methods used for impurity control in the specification.

6. ACTIVE SUBSTANCE SPECIFICATION

6.1 The tests applied and the limits thereby imposed should be stated for:

– physical characteristics,

– tests for identity,

– standards for purity and limitation of impurities,

– standards and tests for potency.

6.2 Analytical methods employed should be described in detail.

7. BATCH ANALYSIS

Data should be provided in this section to illustrate the actual results which have been obtained from routine quality control of the active substance. Results should be given, if possible, for:

– batches of material used in the toxicity tests and clinical trials reported in support of the application,

– recent consecutive batches (5) which are representative of the product which will be supplied for the purposes covered by the marketing authorisation to show that the proposed methods will give routine production material which falls within the

specification limits cited. Information on production batches should be provided, if necessary on an on-going basis.

7.1 Batch analysis results

The results should include:

– date of manufacture,

– batch size and number,

– place of manufacture,

– results of analytical determinations,

– use of batches.

As far as possible, the results should give actual figures for tests on, for example, impurity levels. Results which merely state that the material "complies" with the test are not sufficiently informative, especially where a relatively wide limit is allowed in the specification.

The batch analyses should include all the tests set out in the specification. There may, however, be cases where earlier batches of material were tested using a slightly different specification. In these cases, a brief explanatory note should be included.

7.2 Discussion of results

Any apparently inconsistent or anomalous results in the batch analyses should be explained.

8. REFERENCE STANDARDS

The criteria for establishing the reference substances (primary and secondary) for routine analysis should be given with full analytical profiles.

9. RADIOLABELLED PRODUCT

Information on radiolabelled material should be compatible with the above guidelines.