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Human Medicines Evaluation Unit

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COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

NOTE FOR GUIDANCE ON SUMMARY OF REQUIREMENTS FOR ACTIVE SUBSTANCES IN PART II OF THE DOSSIER

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NOTE: This Note for Guidance is the revision of the Guideline "Requirements in Relation to Active Substances" published in Volume III of the Rules Governing Medicinal Products in the European Union.

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

Note for guidance concerning the application of Part 2, section C of the Annex to Directive 75/318/EEC, as amended, of the data required for the granting of a marketing authorisation.

CLASSIFICATION OF ACTIVE SUBSTANCES

Active substances may be classified into:

- new active substances, cf. definition in the *Notice to Applicants*
- existing active substances not included in the Ph.Eur. or the pharmacopoeia of an EU Member state
- pharmacopoeial active substances included in the Ph.Eur. or the pharmacopoeia of an EU Member State

NEW ACTIVE SUBSTANCES

For new chemical active substances, the requirements are set out in the CPMP guideline *Chemistry of new active substances*, and other CPMP guidelines as mentioned below.

For biotechnologically derived new active substances (as defined in Part A of the Council Regulation (EEC) 2309/93), the requirements are described in the guidelines in Volume III of *The Rules Governing Medicinal Products in the European Union* (e.g. rDNA products, monoclonal antibodies, Notice to applicants) and in the European Pharmacopoeia.

The information may be supplied either as part of the marketing authorisation (MA) application or using the European Drug Master File Procedure (see separate guideline). In the latter case the Applicants Part of the DMF and the critical appraisal need to be included as part of the MA application.

EXISTING ACTIVE SUBSTANCES NOT INCLUDED IN THE PH.EUR. OR A PHARMACOPOEIA OF AN EU MEMBER STATE

In principle, the requirements are as set out above for new chemical active substances.

In all cases the possible content of any residual solvents should be discussed and where appropriate limits for such solvents should be given in line with batch analyses, taking account of the ICH guideline on residual solvents.

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 fully described in the dossier, where necessary).

Where reference is made to the pharmacopoeia of a third country p roof of structure and analytical validation of pharmacopoeial test procedures may be omitted, if justified. 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.

Evidence of the stability of the active substance may be provided from the literature - see separate CPMP guideline on *Stability testing of existing active substances and related finished products.*

The information may be supplied either as part of the marketing authorisation (MA) application or using the European Drug Master File Procedure (see separate guideline). In the latter case the Applicants Part of the DMF needs to be included as part of the MA application.

ACTIVE SUBSTANCES DESCRIBED IN THE EUROPEAN PHARMACOPOEIA OR THE PHARMACOPOEIA OF A MEMBER STATE

These may be divided into:

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

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 the competent authority to demonstrate the suitability of the pharmacopoeial monograph to assess the quality of the material from the named manufacturer. The use of the EDMF procedure is restricted to the provisions of the Council Directive 75/318/EEC as amended.

In each case the possible content of any residual solvents should be discussed and where appropriate limits for such solvents should be given in line with batch analyses, taking account of the ICH guideline on residual solvents, cf. European Pharmacopoeia general chapter on residual solvents.

In all cases the possible need for stability studies should be considered, cf. CPMP guideline *Stability testing of existing active substances and related finished products.*

In relation to solid-state properties, the official pharmacopoeial monographs are intended to control the general suitability of active substances for any of the likely intended uses. 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), a suitable specification must be proposed with details of test methods, batch analyses, validation data etc.

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 additional to those of the pharmacopoeial monograph should be supplied to the competent authority. A European Pharmacopoeia Certificate may be supplied.

Herbal drugs and herbal drug preparations: In the case of herbal drugs and herbal drug preparations, 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 and fumigants). In that case, details of the tests additional to those of the pharmacopoeial monograph should be supplied to the competent authority.

Biotechnologically derived products: In the case of biotechnologically derived substances, full information should be supplied, and in particular information on the manufacture of the substance, measures to ensure freedom from potentially pathogenic agents and stability shall be provided to the competent authority. The information may be supplied either as part of the marketing authorisation (MA) application or using the European Drug Master File Procedure (see separate guideline). In the latter case the Applicants Part of the DMF needs to be included as part of the MA application.

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 and stability shall be provided to the competent authorities. The information may be supplied in the form of a Certificate of suitability from the European Pharmacopoeias or, alternatively, either as part of the marketing authorisation (MA) application or using the European Drug Master File Procedure (see separate guideline). In the latter case the Applicants Part of the DMF needs to be included as part of the MA application.

Organic substances (synthetic or semi-synthetic or isolated from herbal sources or from micro-organisms): In relation to 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 to test for those impurities, most likely to arise during synthesis, should, in all cases, be demonstrated to the competent authorities. The suitability may be shown in one of the following four ways. The preference of the competent authorities will be option 1, but options 2-4 may be chosen.

1. Certificate of suitability of the pharmacopoeial monograph

The manufacturer of the active substance 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 1 of the Council of Europe Resolution AP-CSP (96) 5 *Certification of suitability to the monographs of the European Pharmacopoeia.*

The applicant should include a copy of the Certificate of Suitability in the dossier (section IIC), together with a written assurance that no significant changes in the manufacturing method have taken place since the date of certification.

The certificate will not necessarily address any need for controlling physico-chemical characteristics such as particle size etc.

2. Full details of manufacture

The MA Applicant may submit full details on the active substance, its manufacture, control etc. as outlined in the guideline *Chemistry of the active substance*. However, proof of structure may not be necessary where this can be shown by specific identification tests in relation to reference substances fully described in the dossier, where necessary. Similarly, stability information may not be necessary where adequate literature evidence can be cited and summarised as indicated in the separate CPMP guideline on *Stability tests on existing active substances and related finished products*. 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 pharmacopoeial monograph. In the case of a monograph containing a transparency note, this note should be compared to list of

potential impurities given in the dossier. In case that not all potential impurities are mentioned in a transparency note the MA Applicant should demonstrate whether the tests of the monograph can control these *new* impurities, *and the toxicological implications should be addressed*. All recurring impurities in amounts at or above 0.1% (for toxic impurities possibly even at lower levels) should be subject to the above discussion.

3. European Drug Master File

The full details of manufacture may be submitted as a Drug Master File as outlined in the CPMP guideline *European Drug Master File Procedure for Active Substances*. In such case the Applicants Part should be included in the MA Applicants dossier. In the dossier and/or in the Expert report a thorough discussion should be included to demonstrate whether the pharmacopoeial monograph tests are in fact able to control all recurring impurities at or above 0.1%, and resulting toxicological implications should be addressed.

4. Other evidence of suitability of the pharmacopoeial monograph

The applicant may supply other evidence obtained from the active ingredient manufacturer (AIM). This may include the following evidence

a) information as to the length of time that the particular named source has been on sale in the European Union and elsewhere; and

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; and

c) evidence that samples from the named source had been supplied to the Ph.Eur. Commission or national Pharmacopoeia Commission and have been taken into account in the development of their monograph; and

d) a statement that no additional tests arising from the use of the manufacturing route were necessary in order to identify and limit additional impurities at or above 0.1% (for toxic impurities at even lower levels where appropriate) not specifically controlled by the pharmacopoeial monograph.

The above is one possible approach to providing reassurance to the authorities of the suitability of the pharmacopoeial monograph to control a well-defined active substance with long and safe patient exposure from the named source. It is noted, however, that even when a monograph has been in force for many years, it will not necessarily be sufficient in relation to a new route of synthesis.