EXCIPIENTS IN THE DOSSIER FOR APPLICATION FOR MARKETING AUTHORISATION OF A MEDICINAL PRODUCT

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INTRODUCTION

This note for guidance is concerned with the application to excipients of Part 2, sections A, C, E, F of the annex to Directive 75/318/EEC as amended with a view to the granting of a marketing authorisation for a new medicinal product.

The data should be presented according to the standard format described in the Notice to Applicants (Volume II of "*The Rules Governing Medicinal Products in the European Union*" series), parts II A, C, E and F.

PART 2.A.1 COMPOSITION OF THE MEDICINAL PRODUCT

Excipients must be listed, specifying their common name, their quantity and the use and reference to any relevant standard. When the common name is not sufficient to indicate functional specifications, the brand name with commercial grade should be specified. In the case of excipients presented as a mixture of compounds, details as to the composition should be provided in qualitative and quantitative terms. However, for flavouring agents and aromatic substances, it is permitted to give the qualitative composition only.

PART 2.A.4 DEVELOPMENT PHARMACEUTICS

This section should comprise an explanation of the choice of the excipient (and grade where necessary) according to the note for guidance *Development Pharmaceutics and Process Validation*.

PART 2.C.2 EXCIPIENTS

Examples of different kinds of excipients are given in the annex.

2.1 Specifications and routine tests

2.1.1 Excipients described in the European Pharmacopoeia or, failing this, in the pharmacopoeia of a Member State

The routine tests which are to be carried out on each batch of starting materials must be stated in the application for marketing authorisation. If tests other than those mentioned in the pharmacopoeia are used, proof must be supplied that the test methods used are suitable to establish that the starting materials meet the quality requirements of that pharmacopoeia. When the monograph covers a family of related products, the particular specifications chosen for the excipients must be submitted. In addition and when necessary, the test used to

determine the quality of the excipient should be shown to be in relation to the function that it fulfils in the medicinal product.

Data on microbiological contamination of the excipients used in the manufacture of sterile products should always be given where membrane filtration is used to achieve sterility.

2.1.2 Excipients not described in the European Pharmacopoeia or in the pharmacopoeia of a Member State

The entire routine test procedure and storage conditions must follow on from the scientific data (2.2.2): an appropriate specification of the excipient must be established, based on the following types of tests:

- Physical characteristics
- Identification tests
- Purity tests, including limits for total or individual impurities, which should be named. Purity tests may be physical, chemical, biological and, if appropriate, immunological.

Where sterile filtration is used in the manufacture of a parenteral medicinal product, data and routine tests on microbiological contamination of excipients should always be given.

- Other relevant tests including, e.g. the tests on parameters which may influence the performance of the dosage form.
- Assay or limit tests if necessary.

2.2 Scientific data

This documentation has an important role to play in justifying the choice and use of an excipient which is used for a particular purpose: it will determine the properties which must be checked during the routine tests and which will be the subject of certain specifications in connection with the bioavailability of the product (see note for guidance: *Specifications and Control Tests on the Finished Product*).

Nevertheless, scientific data are not systematically required for well-known excipients. For example, they are not required for excipients which have been used in similar medicinal products for a long period of time and when their characteristics and properties have not changed significantly.

For solid and semi-solid dosage forms, the scientific data should, if necessary, provide information on the relevant characteristics of the excipient. Special tests are often necessary (e.g. to verify the capacity of the excipient to emulsify and disperse, or to measure the viscosity...).

Appropriate data are needed for excipients used in a new route of administration.

2.2.1 Scientific data on excipients already included in the European Pharmacopoeia, or failing this, in the pharmacopoeia of a Member State and other well-known excipients already used in a medicinal product

For these excipients, scientific data will normally not be required. However, any particular specification concerning the characteristics, as defined in Part 2.A.4, should be justified (e.g. sieve analysis, in relation to microcrystallinity).

2.2.2 Other excipients: a dossier should be established containing the same data as required for new active substances:

a) A strict definition of the excipient, its function and its conditions of use. If the excipient is complex or is made of a mixture of compounds, the composition must be specified in qualitative and quantitative terms.

b) For new excipients and for excipients presented as a mixture of compounds the following should be taken into consideration:

   i. Any bibliographical data on the chemistry and on the toxicology and the field in which the product is already used.

   ii. The Community provisions concerning additives in foodstuffs: any criteria which are based on the toxicological data, with cross-references to these data.

   The quality specifications which have been laid down in the directives are satisfactory as long as the routine control tests used are validated.

   iii. The international specifications (FAO/WHO/JECFA), and other publications such as the Food Chemical Codex.

   iv. For medicinal products for topical use, data on the starting material in cosmetic products (Directive 76/768/EEC).

   v. Data concerning the toxicology of the new excipient should be presented according to the dosage form and the route of administration of the medicinal product (if applicable).

c) Documentation on chemistry of excipients is required for all new excipients, taking as its basis the note for guidance *Chemistry of Active Substances*.

   - The origin of the excipient, including the name and address of manufacturer.
   - A general outline of the synthesis (manufacture and purification).
   - Structure.
   - Physical, chemical properties, identification and purity tests.
   - Validated methods of analysis with a presentation of batch results.
   - Miscellaneous information (microbiological tests, etc.).
   - Contamination, presence of foreign substances, residual solvents, etc.
   - In the case of an excipient obtained from a mixture of several components, the quality of each component and the physico-chemical tests for the mixture should be described.

The routine test procedures and limits should be established on the basis of the documentation given in the dossier.

PART 2.E THE FINISHED PRODUCT

Apart from those situations envisaged in the note for guidance *Specifications and Control tests on the Finished Product* it is not usually necessary to carry out identity testing and an assay of the excipients in the finished product at release.

1. Stability tests on starting materials

For new excipients, stability data should be provided as required for new active substances.

2. Stability tests on the finished product

The maintenance of the physico-chemical properties of the finished product are dependent upon the properties and the stability of the excipients (see note for guidance *Specifications and Control Tests on the Finished Product*).

ANNEX

Examples of requirements concerning different kinds of excipients

1. Excipients which are a single chemical entity include, for example, organic and inorganic acids and their salts, sugars and alcohols.

   They may have undergone physical treatments which gave them special technological characteristics (e.g. micronisation).

2. Chemically transformed excipients include excipients which have undergone a special chemical treatment in order to confer certain technological characteristics (e.g. modified starch).

   The name and quality of such excipients should be defined in such a way as to avoid confusion with an unmodified excipient.

3. Mixtures of chemically related components include, for example, polyol esters (mixture of mono, di and tri esters), hydrogenated glucose syrup, maltitol syrup.

   For these products the dossier should specify the following characteristics of the excipient:

   - the nature and content of each component with a statement of its acceptable limits;
   - technological criteria (appropriate criteria to the performance of dosage form);
   - any additives which may be present.

4. Mixed excipients are ready-for-use preparations, for example for direct compression or film coating.

   - The qualitative and quantitative composition of the mixed excipient should be submitted, the specifications of the product as a whole and of each component must be stated.

5. Excipients of natural origin, so called “natural” products have often undergone some kind of chemical treatment.

   In general and if relevant for the quality control of the product, data should give an outline of the operations carried out to obtain and to purify the product, and any special characteristics: decomposition products, specific impurities, chemical substances used during the treatment with residual limits, methods of sterilisation or decontamination, with a description of the effect of these processes on the excipient (e.g. modification of the physical structure).

6. For biological excipients of animal or human origin, the risk of transmitting adventitious agents should be considered and appropriate documentation submitted (e.g.; method of preparation and control of tissues and body fluids used as starting materials). In addition, the name of the manufacturer and site of manufacture should be specified.

7. Flavouring agents (flavours and aromatic substances) are either natural products and/or products obtained by chemical synthesis. Because of the complexity of their composition, it is only necessary to describe the general qualitative composition mentioning the main constituents with an appropriate process of identification to ensure the consistency of the composition (in particular, identification of the main constituents and if necessary carriers).

   Most constituents of artificial flavours have internationally accepted purity criteria in food use (FAO/WHO). Reference to these standards is acceptable for medicinal products.

8. Colouring matters: Community legislation on colouring matters in foodstuffs and medicinal products is applicable.