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Guideline on excipients in the dossier for application for marketing authorisation for veterinary medicinal products

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*The current revision consists of administrative changes made in order to align the guideline with Regulation (EU) 2019/6 and to align with the current EMA template for Guidance. The references to the legislation applicable and other scientific guidelines have also been updated as appropriate. As no changes were made to the scientific content, no concept paper and no public consultation were deemed necessary. The document reference number is changed to ensure correct document management. The former document reference number is EMEA/CVMP/004/98.

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Guideline on excipients in the dossier for applications for marketing authorisation in veterinary medicinal products

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Introduction

This guideline is concerned with the application to excipients of Annex II to Regulation (EU) 2019/6, as amended, with a view to granting a marketing authorisation for a veterinary medicinal product.

PART 2.A.1: Qualitative and quantitative composition

Excipients must be listed, specifying the name of the European Pharmacopoeia, the name of the national pharmacopoeia of one of the Member States, the international non-proprietary name recommended by WHO, or, failing this, the exact scientific designation. Excipients not having an international non-proprietary name or an exact scientific designation shall be described by a statement of how and from what they were prepared, supplemented, where appropriate, by any other relevant details. For preservatives and colouring matter, the Union E-number for colouring agents should be provided.

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 permissible to provide the qualitative composition only.

PART 2.A.2: Product Development

This section should comprise an explanation of the choice of the excipient (and grade where necessary) according to the Guideline on development pharmaceutics for veterinary medicinal products.

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 a pharmacopoeia

The routine tests which are to be carried out on each batch of starting material must be stated in the application for marketing authorisation.

If tests other than those mentioned in the pharmacopoeia are used, evidence should be supplied to confirm that the test methods used are suitable to establish that the excipient meets the quality requirements of the pharmacopoeia. When the monograph covers a family of related products, the particular specifications chosen for the excipient must be submitted. When necessary, information on additional tests used to determine the quality of the excipient in relation to the function that it fulfils in the veterinary medicinal product should be submitted.

In cases where the excipient is not described in the European Pharmacopoeia nor in the pharmacopoeia of a Member State, compliance with the monograph of a third country pharmacopoeia may be accepted. In such cases, the applicant shall submit a copy of the monograph accompanied by a translation where appropriate.

Data on microbiological contamination of the excipients used in the manufacture of sterile products should always be given.

2.1.2 Excipients not described in a pharmacopoeia

The routine test procedures and storage conditions must be in accordance with the scientific data (2.2.2): an appropriate specification of the excipient must be established, based on the following types of tests:

a) Physical characteristics

b) Identification tests

c) Purity tests, including limits for total or individual impurities, which should be named. Purity tests may be physical, chemical, biological and, if appropriate, immunological. Data on microbiological contamination of the excipients used in the manufacture of sterile products should always be given.

d) Other relevant tests including, e.g. tests on parameters which may influence the performance of the dosage form (for example particle size, viscosity,).

e) 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 other veterinary and human medicinal products for a long period of time.

The routine tests to be carried out on each batch of excipient are to be described by the applicant.

Additional data may be needed for excipients used by a new route of administration or in a new target species (to be decided on a case-by-case basis).

For toxicological and residue aspects, a cross-reference should be made to the safety part of the marketing authorisation application.

2.2.1 Excipients included in a pharmacopoeia

For these excipients, scientific data will normally not be required. However, where an excipient in the European Pharmacopoeia or in the pharmacopoeia of the Member State has been prepared by a method liable to leave impurities not controlled in the pharmacopoeia monograph, these impurities and their maximum tolerance limits should be declared and suitable test procedures described.

Any particular specification concerning the characteristics, defined in Part 2.A.2 Product development, should be justified (e.g. sieve analysis).

For excipients not described in the European Pharmacopoeia nor in the pharmacopoeia of a Member State, the applicant shall submit, where necessary, the validation of the test procedures contained in the monograph used.

2.2.2 Other new excipients or new excipients presented as a mixture of compounds.

A dossier should be established containing the same data as required for new active ingredients;

a) A full characterisation of the excipient, with an explanation of its function should be presented. If the excipient is complex or is made of a mixture of compounds, the composition must be specified in qualitative and quantitative terms.

b) The following data should be provided (if applicable):

   i) Any bibliographical data on the chemistry and on the toxicology and the field in which the product is already used (cross-reference to the safety part of the marketing authorisation application).

   ii) The Union provisions concerning additives in foodstuffs: any criteria which are based on toxicology data, with cross-references to these data. The quality specifications which have been laid down in the Directives will generally be satisfactory as long as the routine control tests used are validated. However, for e.g. injectables, further tests may be required.

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

   iv) For veterinary medicinal products for topical use, data on the use of the excipient in cosmetic products (Regulation (EC) No 1223/2009).

   v) Data concerning the toxicology of the new excipient should be presented according to the dosage form, the route of administration and the target species of the veterinary medicinal product.

c) Documentation on the chemistry of excipients is required for new excipients in a veterinary medicinal product, taking as its basis the Guideline on the chemistry of active substances for veterinary medicinal products;

   I. The origin of the excipient, including the name and address of the manufacturer.

   II. A general outline of the synthesis.

   III. Structure.

   IV. Physical and chemical properties, identification and purity tests.

   V. Validated methods of analysis with a presentation of batch results.

   VI. Miscellaneous information (microbiological tests, etc.).

   VII. Contamination (presence of foreign substances, residual solvents, etc.).

   VIII. 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: Control tests on the finished product

Apart from those situations envisaged in the Guideline on Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (VICH GL39) and in the Annex II to Regulation (EU) 2019/6, as amended, it is not usually necessary to carry out identity testing or an assay of the excipients in the finished product at release.

PART 2.F Stability test

1. Stability Tests on New Excipients

For new excipients, stability data should be provided as required for new active substances and a re-test period should be proposed.

2. Stability Tests on the Finished Product

The maintenance of the physico-chemical properties of the finished product are dependent upon the properties and stability of the excipients (see Guideline on Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (VICH GL39) and Annex II to Regulation (EU) 2019/6, as amended).

Annex

Examples of requirements concerning different kinds of excipients

1. Excipients that 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 give 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 an excipient 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;
- appropriate technological criteria that may affect the performance of the dosage form;
- any additives which may be present.

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

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.

For each component of the mixed excipient described in a pharmacopoeia, the monograph should be applied.

5. Excipients of natural origin and so called "natural" products, which may have undergone some kind of chemical treatment.

In general, and if relevant for the quality control of the product, the 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. Biological excipients of animal or human origin

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

7. Flavouring agents

Flavouring agents (flavours and aromatic substances) are either natural products 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 veterinary medicinal products.

8. Colouring matters

Union legislation on colouring matters in foodstuffs and veterinary medicinal products is applicable.