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

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For human medicinal products, this Guideline replaces the Guideline on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Products (Eudralex 3AQ9a) and the Note for Guidance on Inclusion of Antioxidants and Antimicrobial Preservatives in Medicinal Products (CPMP/CVMP/QWP/115/95).

The latter Guideline remains a CVMP guideline and remains applicable to Veterinary products.

KEYWORDS	excipients, human, novel excipient, antioxidant, preservative

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

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EXECUTIVE SUMMARY

This guideline describes the information that needs to be submitted in relation to excipients including antioxidants and antimicrobial preservatives, in the context of applications for marketing authorisations or variations relating to an excipient in authorised medicinal products.

1. INTRODUCTION (BACKGROUND)

Excipients are the constituents of a pharmaceutical form apart from the active substance.

Excipients include e.g. fillers, disintegrants, lubricants, colouring matters, antioxidants, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, solubilisers, permeation enhancers, flavouring and aromatic substances etc., as well as the constituents of the outer covering of the medicinal products, e.g. gelatine capsules.

Examples of different types of excipients are given in annex 1. Information on the excipients used in a medicinal product should be provided in part 3.2.P.1, 3.2.P.2, 3.2.P.4 and 3.2.A.3 of the dossier.

Excipients to be used in formulations for the paediatric population should be selected with special care. Possible sensitivities of the different age groups should be taken into consideration. For example, colouring agents with documented safety risks, e.g. azo dyes and other synthetic colouring agents, should not be used in medicinal products for paediatric use when only intended for aesthetic purposes.

Antioxidants are excipients which are used to improve stability of medicines by delaying the oxidation of active substances and other excipients. Antimicrobial preservatives are normally added to prevent microbial proliferation arising under in use conditions. These properties are due to certain chemical groups which are usually harmful to living cells and might therefore be associated with certain risks when used in humans. Thus inclusion of antimicrobial preservatives or antioxidants in a medicinal product needs special justification. Wherever possible the use of these substances should be avoided, particularly in case of paediatric formulations. The concentration used should be at the lowest feasible level. Further information is given in annex 2.

Parenteral infusions should not contain added antimicrobial preservatives. Antimicrobial preservatives must not be added to medicinal products intended for use by any route of administration that will give access to the cerebrospinal fluid or in products that will be injected retro-ocularly.

Permeation enhancers are excipients which have the ability to modify the penetration of active substances through the skin and therefore could influence significantly the in-vivo performance of a transdermal formulation. Information and control of these substances is essential for all transdermal formulations, where a constant and persistent release of active substances over several hours, or even days, is necessary for therapeutic efficacy. Further information is given in annex 3.

2. SCOPE

This guideline is applicable to all excipients in medicinal products for human use, in the context of applications for marketing authorisations or variations relating to an excipient in authorised medicinal products.

The guideline does not apply to excipients used in products in the clinical research stages of drug development. However, the principles in this guideline are important to consider during those stages as well.

The data should be presented according to the standard format described in the Common Technical Document (CTD) Module 3 sections P.1, P.2, P.4, P.5, P.8 and A.3.

Directive 2001/83/EC, as amended

4. MAIN GUIDELINE TEXT

4.1 Description and Composition of the Drug Product (3.2.P.1)

Excipients should be listed specifying their common name, the quantity present, their function and a reference to a relevant standard. When the common name is not sufficient to indicate functional properties, the brand name with commercial grade should be specified. In the case of excipients presented as a mixture of compounds, details of the composition should be provided in qualitative and quantitative terms. However, for flavouring agents it is allowed to state the qualitative composition only.

4.2 Pharmaceutical Development (3.2.P.2)

According to the Notes for Guidance on Pharmaceutical Development (CHMP/ICH/167068/04 and CHMP/QWP/055/96), this section should include an explanation of the choice of the excipient(s) (and grade where necessary). Compatibility of the excipients with active substances and, where relevant, with other excipients, should be established. The excipients chosen, their concentration, and the characteristics that can influence the drug product performance (e.g., stability, bioavailability) or manufacturability should be discussed in relation to the respective function of each excipient. Tests in addition to the pharmacopoeial ones, identified through development, should be described in section 3.2.P.4.2 and 3.2.P.4.3.

4.3 Specifications (3.2.P.4.1)

Colouring matters shall, in all cases, satisfy the requirements of Directives 78/25/EEC, as amended and/or 94/36/EC (colours for use in foodstuffs). In addition, colouring matters in medicinal products have to comply with the specifications of the Annex of Directive 95/45/EC, laying down specific purity criteria concerning colours for use in foodstuffs.

The references in Directive 78/25/EEC, as amended are interpreted in a way, which permits the use in medicinal products of all colourants mentioned in Annex I of Directive 94/36/EC.

The bioburden and, where relevant, the endotoxin limits for excipients used in the manufacture of sterile medicinal products shall be stated. However, if bioburden/endotoxin content of the bulk solution prior to sterilisation is checked using appropriate in process controls, the testing of the individual excipient may be omitted.

Data concerning residual solvents in excipients should be submitted in accordance with the Note for Guidance on Impurities: Residual Solvents (CPMP/ICH/283/95).

a) Excipients described in the European Pharmacopoeia or in the pharmacopoeia of an EU Member State

Reference to the current edition of the pharmacopoeia should be included in the dossier for marketing authorisation. When the monograph covers a group of related materials (i.e. polymers), the particular specification chosen for the excipient, should be submitted, together with the rationale for its selection. If tests other than those mentioned in the pharmacopoeia are used, proof should be supplied that the test methods are at least equivalent to those described in the pharmacopoeia (see European Pharmacopoeia, 1.1. General Statements). It may be necessary to add tests and acceptance criteria to the pharmacopoeial specification, depending on the intended use of the excipient (functionality-related characteristics).

b) Excipients described in a third country pharmacopoeia

Where an excipient is neither described in the European Pharmacopoeia nor in the pharmacopoeia of a Member State, compliance with the monograph of a third country pharmacopoeia (e.g. United States Pharmacopoeia/National Formulary and Japanese Pharmacopoeia) can be accepted.

The applicant should justify the reference to such pharmacopoeia and submit justified specifications in accordance with the general monograph of the European Pharmacopoeia: Substances for Pharmaceutical use.

c) Excipients not described in any pharmacopoeia

An appropriate specification for the excipient should be established, based on the following types of tests:

- Physical characteristics
- Identification tests
- Purity tests, including limits for total and individual impurities, which should be named, e.g. by reference to a chromatographic relative retention time. Purity tests may be physical, chemical, biological and, if appropriate, immunological.
- Assay or limit tests if necessary and corresponding validation parameters.
- Other relevant tests e.g. tests on parameters (quantitative), which have been determined to influence the performance of the dosage form.

4.4 Justification of Specifications (3.2.P.4.4)

Justification of a specification takes into account the choice and particular use of the excipient (see Note for Guidance on Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (CPMP/ICH/367/96)).

For excipients described in the European Pharmacopoeia, or in the pharmacopoeia of an EU Member State, justification of specifications will normally not be required. However, any particular acceptance criteria concerning the characteristics, as defined in Section 3.2.P.2.1.2, should be justified (e.g. particle size testing of a micronised substance). In addition, justification of a specification is not systematically required for well-known excipients. For example, it is 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.

Where critical, the justification of specifications should provide information on excipient characteristics relevant to the medicinal product performance. For example, for solid and semi-solid dosage forms, special tests may be necessary to demonstrate the capability of the excipient to emulsify and disperse, or to provide appropriate viscosity (Functionality related characteristics).

4.5 Excipients of Human or Animal Origin (3.2.P.4.5)

Viral Safety and TSE Risk should be documented in accordance with the relevant directives and guidelines (see European Pharmacopoeia General Chapter 5.1.7 Viral Safety and 5.2.8. Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products).

4.6 Novel Excipients (3.2.P.4.6)

Full details of manufacture, characterisation and controls with cross references to supporting safety data should be provided for novel excipients, according to the drug substance format.

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