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# COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

**DRAFT**

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

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This Guideline replaces the Guideline on Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Products (Eudralex 3AQ9a) and CPMP 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 applicable to Veterinary products.

Due to the long time elapsed after the first release for consultation of the draft guideline and substantial changes introduced to the guideline structure following comments received, it has been agreed to re-release the draft guideline for further 3 months public consultation.

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| **KEYWORDS** | excipients, human, novel excipient, antioxidant |

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

**TABLE OF CONTENTS**

## 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 or variations to marketing authorisations.

## 1. INTRODUCTION (BACKGROUND)

Excipients may be defined as the constituents of a pharmaceutical form that are not the active substance. According to their function, these constituents can be classified as technological, applicatory, stabilising or biopharmaceutical excipients.

Excipients include e.g. colouring matters, antioxidants, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, solubilisers, permeation enhancers, flavouring and aromatic substances as well 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 finished product should be provided in part 3.2.P.4 of the dossier.

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. The properties are due to certain chemical groups which are usually harmful to living cells and might therefore be associated to certain risks when used in man. Thus inclusion of antimicrobial preservatives or antioxidants in a finished product needs special justification. The use of these substances should be avoided in general, especially when considering the suitability of related formulations to the paediatric population.

Parenteral infusions should not contain added antimicrobial preservatives. Antimicrobial preservatives must not be added to 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 significantly could influence 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 mandatory for therapeutic efficacy.

## 2. SCOPE

This guideline is applicable to all excipients including antioxidants and antimicrobial preservatives in medicinal products for human use with a view to applying for or amending a related marketing authorisation. The data should be presented according to the standard format described in the Common Technical Document (CTD) Module 3, part P, sections P.1, P.2, P.4, P.5 and P.8.

## 3. LEGAL BASIS

Directive 2001/83/EC, as amended

Directive 2003/63/EC.

## 4. MAIN GUIDELINE TEXT

### 4.1 Pharmaceutical Development (3.2.P.2)

According to the ICH Q8 Note for Guidance on Pharmaceutical Development (CHMP/ICH/167068/04), this section should comprise an explanation of the choice of the excipient

(and grade where necessary). Compatibility of excipients with other excipients and active substances should be established.

**4.2 Specifications (3.2.P.4.1)**

Colouring matters shall, in all cases, satisfy the requirements of Directives 78/25/EEC 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 can be interpreted in a way, which would permit the use in medicinal products of all colourants mentioned in Annex I of Directive 94/36/EC.

The bioburden limits for excipients used in the manufacture of sterile products shall be stated when membrane filtration is used in the manufacture of sterile products. The limits shall be established in accordance with available validation data for the process.

Data concerning the residual solvents in excipients should be submitted in accordance with ICH Q3C 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**

The tests which are to be carried out on each batch of excipient should be stated in the application for marketing authorization. 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 as described in the pharmacopoeia (see European Pharmacopoeia, 1.1. General Statements).

When the monograph covers a family of related materials, the particular specification chosen for the excipient should be submitted, together with the rationale for its selection. It may be necessary to add tests and acceptance criteria to the pharmacopoeial specification, depending on the intended use of the excipient (functionality testing).

**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; in such cases, the applicant shall submit a copy of the monograph accompanied by the validation of the test procedures contained in the monograph and a translation where appropriate.

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 of the excipient should 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.
- Other relevant tests including, e.g. the tests (quantitative) on parameters which have been determined to influence the performance of the dosage form.
- Assay or limit tests if necessary and corresponding validation parameters.

### 4.3 Justification of Specifications (3.2.P.4.4)

Justification of a specification takes into account the choice and particular use of the excipient: it will determine the properties which should be checked during the routine tests and which will be the subject of certain acceptance criteria in connection with the bioavailability of the product (see ICH Q6A 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 if not described in the Ph. Eur., 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. sieve analysis, in relation to microcrystallinity). 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 appropriate, the justification of specifications should provide information on characteristics of the excipient relevant to the medicinal product's 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 tests).

### 4.4 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).

### 4.5 Novel Excipients (3.2.P.4.6)

For novel 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 should be specified in qualitative and quantitative terms.

b) For novel 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 cutaneous use, data on the starting material in cosmetic products (see Directive 76/768/EEC, as amended).

   v. Data concerning the toxicology of the novel 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 CPMP Guideline on the Chemistry of New Active Substances (CPMP/QWP/130/96).

- 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.
- Stability data should be provided as required for the active substances in the ICH Q1A Note for Guidance on Stability Testing of New Drug Substances and Products (CPMP/ICH/2736/99).

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

### 4.6 Control of Drug Product (3.2.P.5)

Apart from those situations envisaged in the ICH Q6A Note for Guidance on Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (CPMP/ICH/367/96), it is not usually necessary to carry out identity testing and an assay of the excipients in the finished product at release. The control of antioxidants and antimicrobial preservatives, however, should comply with the requirements outlined in the ICH guideline mentioned above.

The finished product release specifications should include an identification test and a content determination test with acceptance criteria and limits for each antioxidant and antimicrobial preservative present in the formulation. The finished product shelf-life specification should also include an identification test and limits for the antimicrobial preservatives present.

Where antioxidants are used up during the manufacture of the product, the release limits should be justified by batch data. The adequacy of specified limits should be justified on the basis of controlled conditions and in-use stability testing to ensure that sufficient antioxidant remains to protect the product throughout its entire shelf-life and during the proposed in-use period.

### 4.7 Stability (3.2.P.8)

The maintenance of the physico-chemical properties of the finished product are partly dependent upon the properties and the stability of the excipients

For the drug product the application should follow the current CHMP/QWP stability guidelines and should ensure that antimicrobial preservative and antioxidants levels are quantified periodically throughout the shelf-life. Testing of the antimicrobial preservative content throughout shelf life should be performed to ensure that antimicrobial preservative levels remain above the level challenged for preservative efficacy.

In the case of products presented in multidose containers, the efficacy of the antimicrobial preservative under simulated in-use conditions should be established. The tests should be performed under the same condition as it is expected to be used by the end user. It may also be appropriate to examine the efficacy of the antimicrobial preservative following storage of opened or used containers for the proposed in use shelf-life.

### 4.8 Labelling

For all excipients included in a finished product, the relevant guidance documents: Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 3B "Excipients in the Label and Package leaflet of Medicinal Products for Human Use" (Eudralex 3BC7A) and CPMP Position Paper on Thiomersal, Implementation of the Warning Statement Relating to Sensitisation (CPMP/2612/99) have to be taken into account.

However, if a product is presented in a multidose container without an antimicrobial preservative because:

a) it is intended for single use only (e.g. cytotoxic),

b) the product is self-preserving,

c) the product is oils based,

d) the container closure system is able to prevent microbial ingress into the formulation

the labelling and product literature should indicate the absence of an antimicrobial preservative. This would not only emphasise the increased risk associated with the use of such products, but also aid the physician to specifically identify a product without an antimicrobial preservative.

## DEFINITIONS

Functionality related test: Control of additional properties (e.g. physical characteristics, functionality-related characteristics) may be necessary for individual manufacturing processes or formulations.

Novel excipient: A novel excipient may be a new chemical entity or a well established one but which has not yet been used for human administration and /or for a particular human administration pathway in the EU and/or outside the EU.

## REFERENCES

This guideline should be read in conjunction with:

- ICH Q6A Note for Guidance on Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (CPMP/ICH/367/96)
- ICH Q3C Note for Guidance on Impurities: Residual Solvents (CPMP/ICH/283/95)
- ICH Q1A Note for Guidance on Stability Testing of New Drug Substances and Products (CPMP/ICH/2736/99)
- Guideline on the Chemistry of New Active Substances (CPMP/QWP/130/96)
- European Pharmacopoeia General Monograph, Substances for Pharmaceutical Use (2034)
- European Pharmacopoeia General Chapter 5.1.3 Efficacy on Antimicrobial Preservation
- European Pharmacopoeia General Chapter 5.1.7 Viral Safety
- Individual monographs of the European Pharmacopoeia
- Note for Guidance on Development Pharmaceutics (CPMP/QWP/155/96)
- ICH Q8 Note for Guidance on Pharmaceutical Development (CHMP/ICH/167068/2004)
- Rules governing Medicinal Products in the European Community, Notice to Applicants, Volume 3B – "Excipients in the Label and Package leaflet of Medicinal Products for Human Use" (Eudralex 3BC7A)
- Note for Guidance on Maximum Shelf-life for Sterile Products for Human Use After First Opening or Following Reconstitution (CPMP/QWP/159/96 corr)
- Note for Guidance on In-use Stability Testing of Human Medicinal Products (CPMP/QWP/2934/99).

**ANNEX 1**

Different Types of excipients and their requirements

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 should 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 material). 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.

**ANNEX 2**

**ANTIOXIDANTS & ANTIMICROBIAL PRESERVATIVES**

For each antioxidant and antimicrobial preservative the application should contain:

- reason for inclusion
- proof of safety and efficacy
- the method of control in finished product
- levels on storage of broached and unbroached containers
- details on the labelling of the finished product

The safety of the antioxidant or antimicrobial preservatives should be supported by bibliographic and/or experimental data.

**ANTIOXIDANTS**

Antioxidants are used to reduce the oxidation of active substances and excipients in the finished product. Antioxidants should not be used to disguise poorly formulated products or inadequate packaging. The need to include an antioxidant should be explained and fully justified. Oxidative degradation can be accelerated by light and by the presence of mineral or metallic impurities, due to the formation of free radicals.

The efficacy obtained for an antioxidants depends on its nature, the stage at which it is incorporated intothe finished product, the nature of the container and the formulation.

Three types of antioxidants.

| Type | Definition | Example |
|---|---|---|
| True antioxidants | These are thought to block chain reactions by reacting with free radicals | Butylated hydroxytoluene (BHT) |
| Reducing agents | These have a lower redox potential than the drug or excipient they are protecting | Ascorbic acid |
| Antioxidants synergists | These enhance the effects of antioxidants | Sodium edetate |

**ANTIMICROBIAL PRESERVATIVES**

Antimicrobial Preservatives are used to prevent or inhibit the growth of micro-organisms which could present a risk of infection or degradation of the medicinal product. These micro-organisms may proliferate during normal conditions of use of the product by the patient, particularly in multidose preparations.

On no account should antimicrobial preservatives be used as an alternative to Good Manufacturing Practice (GMP).

Preparations at greatest risk of contamination are those which contain water such as solutions, suspensions and emulsions to be taken orally, solution for external use, creams and sterile preparations used repeatedly (e.g. injectable multidose preparations and eye-drops).

The level of efficacy will vary according to the chemical structure of the antimicrobial preservative, its concentration, the physical and chemical characteristics of the medicinal product (especially pH) and the type and level of initial microbial contamination. The design of the pack and the temperature at which the product is stored will also affect the activity of any antimicrobial preservatives present.

The antimicrobial efficacy of the antimicrobial preservative in the finished product should be assessed during product development, particularly during stability studies and at the end of the proposed shelf-life, using the method described in the respective Ph. Eur. General Chapter 5.1.3.

If products do not contain an antimicrobial preservative and do not have inherent preservative efficacy they should not be packaged in multidose presentations without a sound justification.

**ANNEX 3**

**SOLUBILISERS AND PERMEATION ENHANCERS**

Solubilisers and permeation enhancers incorporated in transdermal formulations (e.g. transdermal gel or patches) increase or modify the delivery of an active substance into the systemic circulation via the transdermal application route. Strategies to chemically enhance or modify the in-vivo flux comprise disrupture of the stratum corneum structures as well as influencing the thermodynamic activity of an active substance -the driving force for the passive diffusion process- within the formulation (vehicle). The latter one for example can be achieved by solubilisers added to a formulation.

Penetration and permeation performances of active substances in transdermal formulations are furthermore highly dependent on skin site and condition.

The skin condition can be modified by chemical permeation enhancers.

Different types of substances are known for their ability to enhance the permeation through the skin and are commonly used in transdermal formulations. Although representing partly different mechanisms by which they alter the stratum corneum (e.g. extracting lipids from lipid bilayer, partition into bilayers and disrupting its order), those substances have one in common: they increase the active substance diffusity within the barrier membrane after entering the stratum corneum.

Excipients able to modulate the in vivo performance of a transdermal formulation are often not identified and declared as substances with a distinctive influence on the permeation (e.g,: terpene containing oils, declared as fragrances; propylenglykol, declared as solubiliser although permeation enhancing effects can be observed).

Groups of chemical substances known for their ability to act as permeation enhancers or solubilisers in transdermal formulations are for example (list is not exhaustive) surfactants, fatty acids and their salts, fatty esters, alkyl amines, alcohols, azone like molecules, pyrrolidones, sulfoxides and terpenes.

If one of the above mentioned chemical substances is incorporated into a transdermal formulation, a permeation enhancing or influencing effect on the barrier function of the stratum corneum should be assumed, unless otherwise shown by experimental data. The need to include a permeation enhancer or solubiliser and the amount necessary to guarantee constant flux rates should be explained in detail and justified by skin permeation studies during pharmaceutical development. The potential of a permeation enhancer is depending on its concentration and the physico-chemical properties of the respective active substance. It is necessary to evaluate those effects on a case by case basis; no generalization for a certain group of excipients is possible.

A release and shelf life specification -based on the results of clinical or at least permeation studies- needs to be established in order to ensure a reproducible in-vivo performance of the respective formulation.