European Medicines Agency
Inspections

London, 19 June 2007
Doc. Ref. EMEA/CHMP/QWP/396951/2006

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

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

DRAFT AGREED BY QUALITY WORKING PARTY	February 2003
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	February 2003
END OF CONSULTATION (DEADLINE FOR COMMENTS)	August 2003
NEW DRAFT AGREED BY QUALITY WORKING PARTY	September 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	October 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	February 2007
NEW DRAFT AGREED BY QUALITY WORKING PARTY	June 2007
ADOPTION BY CHMP	July 2007
DATE FOR COMING INTO EFFECT	January 2008

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.

3. LEGAL BASIS

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.

a) A detailed description of the excipient, its function and its conditions of use should be provided. If the excipient is complex or consists 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:

- Any bibliographical data on the chemistry and on the toxicology and the field in which the product is already used.
- 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.
- The international specifications (FAO/WHO/JECFA), and other publications, such as the Food Chemical Codex.
- For medicinal products for cutaneous use, data on the ingredient used in cosmetic products (see Directive 76/768/EEC, as amended).
- Data concerning the toxicology of the novel excipient according to the dosage form and the route of administration of the medicinal product (if applicable) in Module 4, the safety section of the dossier.

c) Documentation on chemistry of excipients is required for all novel excipients, taking as its basis the CPMP Guideline on the Chemistry of New Active Substances (CPMP/QWP/130/96) and should include:

- The origin of the excipient, including the name and address of manufacturer.
- A general outline of the manufacturing and purification procedures.
- 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 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.

4.7 Control of Drug Product (3.2.P.5)

Apart from those situations envisaged in the 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 necessary to carry out identity testing and an assay of the excipients in the medicinal product at release. The control of antioxidants and antimicrobial preservatives, however, should comply with the requirements outlined in the guideline mentioned above.

The medicinal 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 medicinal product shelf-life specification should also include limits for antimicrobial preservatives when present.

Where antioxidants are used during the manufacture of the medicinal product, the release limits should be justified by batch data or a sound justification has to be provided, if the proposed specifications do not include an identification test and a content determination test for the antioxidant. If needed, the adequacy of the 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 medicinal product throughout its entire shelf-life and during the proposed in-use period.

4.8 Stability (3.2.P.8)

The maintenance of the physico-chemical properties of the medicinal product is partly dependent upon the properties and the stability of the excipients.

For the medicinal product the application should follow current CHMP/ICH stability guidelines and should ensure that antimicrobial preservative and, if appropriate, antioxidant levels are quantified periodically throughout the shelf-life. The antimicrobial preservative content should be monitored throughout the shelf-life to ensure that antimicrobial preservative levels remain above the level challenged for preservative efficacy and within the specifications.

In the case of non-solid medicinal products presented in multidose containers that contain preservatives, the efficacy of the antimicrobial preservative under simulated in-use conditions should be established. The tests should be performed under conditions simulating the dosage recommendations, as stated in the SPC.

4.9 Labelling

For all excipients included in a medicinal product, the relevant guidance documents: 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.

DEFINITIONS

Novel excipient: A novel excipient is an excipient which is being used for the first time in a drug product, or by a new route of administration (ICH). It may be a new chemical entity or a well established one 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:

- Note for Guidance on Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (CPMP/ICH/367/96)
- Note for Guidance on Impurities: Residual Solvents (CPMP/ICH/283/95)
- 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
- European Pharmacopoeia General Chapter 5.2.8 Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products
- Individual monographs of the European Pharmacopoeia
- Note for Guidance on Development Pharmaceutics (CPMP/QWP/155/96)
- 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 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 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 additive which may be present and their quality if appropriate.

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

   - The qualitative and quantitative composition of the mixed excipient should be submitted, the specifications of the mixture 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. 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.

7. An adjuvant is a substance that helps and enhances the pharmacological effect of a drug or increases the ability of an antigen to stimulate the immune system.

ANNEX 2

ANTIOXIDANTS & ANTIMICROBIAL PRESERVATIVES

For each antioxidant and antimicrobial preservative the application should contain:

- reason for inclusion and justification of level of inclusion
- proof of safety and efficacy
- the method of control in medicinal product (not applicable for synergists e.g. sodium edetate)
- levels on storage of broached and unbroached containers
- details on the labelling of the medicinal product

The safety of the antioxidant or antimicrobial preservatives should be supported by bibliographic and/or experimental data unless the antioxidant or antimicrobial preservative is well known and generally used at same concentrations and by the same route of administration.

ANTIOXIDANTS

Antioxidants are used to reduce the oxidation of active substances and excipients in the medicinal 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 effect obtained from an antioxidant depends on its nature, the stage at which it is incorporated into the medicinal product, the nature of the container and the formulation.

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 to 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, solutions 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 medicinal product should be assessed during product development, and at the end of the proposed shelf-life, using the method described in the respective Ph. Eur. General Chapter 5.1.3.

If non-solid medicinal products do not contain an antimicrobial preservative and do not have self-preserving properties or the container closure system is not able to prevent microbial ingress into the formulation 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) 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 structure (effect on diffusion), alter the solubility of the active substance in the stratum corneum (effect on partition) or influencing the thermodynamic activity of an active substance -the driving force for the passive diffusion process- within the formulation (vehicle). Chemical permeation enhancers can alter the barrier function and the effect can be either reversible or irreversible.

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 or fluidisation of the lipid structure), those substances have one property in common: they increase the active substance permeability through the skin.

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; propylenglycol, 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 can be expected, unless otherwise shown by experimental data. The need to include a permeation enhancer or solubiliser and the amount necessary to guarantee adequate flux rates should be explained in detail and justified by skin permeation studies during pharmaceutical development. The degree of enhancement by a permeation enhancer is depending on its concentration, other excipients in the formulation 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.