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<DRAFT>

NOTE FOR GUIDANCE ON EXCIPIENTS, ANTIOXIDANTS AND ANTIMICROBIAL PRESERVATIVES IN THE DOSSIER FOR APPLICATION FOR MARKETING AUTHORISATION OF A MEDICINAL PRODUCT

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NOTE FOR GUIDANCE ON EXCIPIENTS, ANTIOXIDANTS AND ANTIMICROBIAL PRESERVATIVES IN THE DOSSIER FOR APPLICATION FOR MARKETING AUTHORISATION OF A MEDICINAL PRODUCT

INTRODUCTION

This note for guidance is concerned with the application to excipients, antioxidants and antimicrobial preservatives of Module 3, sections P.1, P.2, P.4, P.5, P.8 of the Common Technical Document with a view to granting a marketing authorisation for a new medicinal product.

The data should be presented according to the standard format described in the CTD Module 3, part P.

Antioxidants and Antimicrobial Preservatives are substances which are used to extend the shelf-life of medicines by respectively retarding the oxidation of active substances and excipients, and by reducing microbial proliferation.

The properties of these substances are due to certain chemical groups which are usually aggressive towards living cells and which lead to certain risks when used in man.

If it is not absolutely necessary to add these substances in medicinal products they must be avoided.

The purpose of this note for guidance is to describe the information that needs to appear in application for marketing authorisations with regards to the addition of any antioxidants or antimicrobial preservatives.

For each antioxidants and antimicrobial preservative the application should contain :

- reason for inclusion
- proof of efficacy
- the method of control in finished product
- details of the labelling of the finished product
- safety information

Several guidelines should be also taken into account :

- ICH Topic Q 6 A : Specifications : Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products : Chemical Substances (3.3.2.2. Oral liquids : d) Antimicrobial preservative content, e) Antioxidants preservative content ; 3.3.2.3. Parenteral Drug Products : g) h) and Decision Tree 8 : Microbiological Attributes of Non-sterile drug products).
- Note for Guidance on Development Pharmaceutics : 3.3. Liquid and Semi-solid Formulations.
- 3BC7A : Excipients in the Label and Package leaflet of Medicinal Products for Human Use
- Note for guidance on maximum shelf-life for sterile products after first opening or following reconstitution.

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SECTION P.1 Description and Composition of the Drug 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.

Antimicrobial preservatives and antioxidants should be chemically defined (reference to existing European Pharmacopoeia monographs may be used) and designated by the Chemical Abstract Service Registry Number (RN-CAS).

The purpose for the inclusion of any antioxidant or microbial preservative should be stated (antioxidant for the benefit of active substance or excipient or both, or antimicrobial preservative).

SECTION P.2 Pharmaceutical development

SECTION P.2.1 Components of the Drug Product

The section P.2.1.2 should comprise an explanation of the choice of the excipient (and grade where necessary) and the level of excipient according to the note for guidance "Development pharmaceutics and process validation".

For antimicrobial preservatives and antioxidants, during the pharmaceutical development of the product the applicant should demonstrate:

- the necessity to add an antioxidant or preservative to the finished product at the chosen level
- the physical and chemical compatibility of the antioxidant and of the preservative with other constituents of the finished product, the container and the closures.

The used concentration must be justified in terms of efficacy and safety, such that the minimum concentration of preservative is used which gives the required level of efficacy. The appropriate test method for efficacy of antimicrobial preservation is that of the European Pharmacopoeia. This should be used to determine whether the required level of activity is achieved.

In the case of antioxidants, these should only be used once it has been shown that their use cannot be avoided, even if the manufacturing process is optimised to minimise the potential for oxidation, for instance by manufacturing and filling products under an inert headspace gas.

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

Some antioxidants or antimicrobial preservatives may be undesirable under certain circumstances :

- mercury containing preservatives : see the CPMP Position Paper on Thiomersal, Implementation of the Warning Statement Relating to Sensitisation (CPMP/2612/99) and EMEA Position Statement on recent developments concerning thiomersal in vaccines (EMEA/CPMP/1578/00). This kind of preservative should be strictly avoided except if no other possibility may be considered but in this case the choice should be fully justified.

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- benzyl alcohol : when used in parenteral products for children under the age of two years. Its degradation product and metabolite is the benzaldehyde, toxic for the CNS.
- Benzoic acid esters (Para hydroxy benzoate and their derivates etc) : when used in any dosage-form for parenteral use.
- Sulphites and Metabisulphites.

Parenteral infusions do not contain any added antimicrobial preservatives and no antimicrobial preservatives are added when the medicinal product is intended for administration by routes where for medical reasons an antimicrobial preservative is unacceptable, such as intercisternally or by any other route of administration which gives access to the cerebrospinal fluid or retro-ocularly.

SECTION P.4 Control of Excipients

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

1. Specifications (P.4.1), Analytical Procedures (P.4.2), Validation of Analytical Procedures (P.4.3) and Justification of Specifications (P.4.4) :

1.1 Excipients described in the European Pharmacopoeia or, if not described in the European Pharmacopoeia, 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.

Antimicrobial preservatives and antioxidants are defined as excipients and as such should be controlled following the rules governing medicinal products in the European Union. These data should be provided in part P.4.

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

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 parental 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.

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* Assay or limit tests if necessary.

When an excipient is not described in the European Pharmacopoeia or in the pharmacopoeia of a Member State or in an other compendium of established use (e.g. USNF Pharmacopoeia and Japanese Pharmacopoeia), validation data of the test methods used should be presented, where appropriate.

1.3 Justification of Specifications

Justifications of specifications takes into account 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, justification of specifications 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 justification of specifications 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.

Justification of specifications on excipients already included in the European Pharmacopoeia, or if not included in the European Pharmacopoeia, in the pharmacopoeia of a Member State and other well-known excipients already used in a medicinal product.

For these excipients, justification of specifications will normally not be required. However, any particular specification concerning the characteristics, as defined in Section P.2.1.2, should be justified (e.g. sieve analysis, in relation to microcrystallinity).

Excipients of Human or Animal Origin (P.4.5)

Viral Safety and TSE Risk should be documented in accordance with the relevant directives.

Novel Excipients (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 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 foodstuff: 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.

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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.

SECTION P.5 Control of Drug 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.

Nevertheless, the finished product release specifications should include an identification test and limits for any antioxidants and antimicrobial preservatives present in the formulation. The finished product specification against which the product is tested throughout its shelf-life should also include 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.

The control of antioxidants and antimicrobial preservatives should comply with the requirements identified in the guideline : ICH Topic Q 6 A : Specifications : Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products : Chemical Substances .

The antimicrobial preservative and antioxidants must be routinely identified and quantified at release.

P.8 Stability

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The maintenance of the physico-chemical properties of the finished product depend on the properties and the stability of the excipients (see note for guidance "Specifications and control tests on the finished product").

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

The application should follow the current QWP/CPMP guidelines on the stability of new dosage forms and should ensure that antimicrobial preservative and antioxidants levels are quantified periodically throughout the shelf-life of the finished product. In addition the efficacy of the preservatives should be established using the European Pharmacopoeia test for efficacy of antimicrobial preservation. This should be performed on the finished product at the end of the shelf-life and at the lower preservative limit in the end of shelf-life specification. The former is necessary, even if no evidence of degradation of the antimicrobial preservative and of the antioxidant is observed on storage, as other chemical and physical changes in the finished product may influence the efficacy of the antimicrobial preservative and the antioxidant.

In the case of products presented in multidose containers, the efficacy of the antimicrobial preservative under simulated in-use conditions must be established. The tests should be performed under the same condition as it is expected to be used by the final 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.

R LABELLING

- Labelling must in accordance with relevant EC directive 2001/83/EC, Note for Guidance : Excipients in the Label and Package leaflet of Medicinal Products for Human Use and CPMP Position Paper on Thiomersal, Implementation of the Warning Statement Relating to Sensitisation (CPMP/2612/99).

However, if a product is presented in a multidose container without a 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,

the labelling and product literature should indicate the absence of a 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 preservative.

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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, maltitolsyrup. 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 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).

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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 medicinal products is applicable.

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.

There are 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

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

The efficacy of antioxidants must be assessed in the finished product in conditions, which simulate actual use by measuring the extent of degradation in the finished product, with and without the antioxidant.

Antioxidants should only be included in a formulation if it has been proven hat their use cannot be avoided. This applies to cases where the manufacturing process is optimised to minimise the potential for oxidation.

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 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 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

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temperature at which the product is stored will also affect of activity of any antimicrobial preservatives present.

The antimicrobial efficacy of the preservative in the finished should be assessed during product development, particularly during stability studies and at the end of the proposed shelf-life, using Pharmacopoeia European test.

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

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