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&
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NOTE FOR GUIDANCE ON INCLUSION OF ANTIOXIDANTS AND ANTIMICROBIAL PRESERVATIVES IN MEDICINAL PRODUCTS

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INCLUSION OF ANTIOXIDANTS AND ANTIMICROBIAL PRESERVATIVES IN MEDICINAL PRODUCTS

1. INTRODUCTION

Antioxidants and Antimicrobial Preservatives are substances which are used to extend the shelf-life of medicines by respectively retarding the oxidation of active ingredients 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 (and animals).

The purpose of this note for guidance is to describe the information that needs to appear in applications for marketing authorisations with regard to the addition of any antioxidants or antimicrobial preservatives. For each antioxidant and antimicrobial preservative the application should contain:

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

2. 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 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
Reducing agents	These have a lower redox potential than the drug or excipient they are protecting	ascorbic acid
Antioxidant synergists	These enhance the effects of antioxidants	sodium edetate

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The efficacy obtained for an antioxidant depends on its nature, its concentration, the stage at which it is incorporated into 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 proved that their use cannot be avoided. This applies to cases where the manufacturing process is optimised to minimise the potential for oxidation.

3. 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-organism may proliferate during normal storage conditions or 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.

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

The antimicrobial efficacy of the preservative in the finished product should be assessed during product development using the European Pharmacopoeia test.

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

4. FORMULATION

Antimicrobial preservative and antioxidants should be chemically defined (reference to existing pharmacopoeia monographs may be used) and designated by the Chemical Abstract Service (CAS) registry number if they are not referenced in the pharmacopoeia.

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

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5. DEVELOPMENT PHARMACEUTICS

During the pharmaceutical development of the product the applicant should demonstrate:

- the necessity to add an antioxidant or a preservative to the finished product at the level chosen.
- 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 concentration used 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 example 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 e.g. mercury containing preservatives, benzyl alcohol (when used in parenteral products for children under the age of 2 years or in newborn animals or in cats), benzoic acid esters (when used in any medicinal products for injection), sulphites and metabisulphite.

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.

6. CONTROL OF THE EXCIPIENTS

Antimicrobial preservatives and antioxidants are defined as excipients and as such should be controlled following the guidance given in The Rules Governing Medicinal Products in the European Union, Volume III “Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product”.

7. CONTROL OF THE FINISHED PRODUCT

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

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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 "Specifications and control testing of the finished product".

8. STABILITY

The application should follow the current CPMP and CVMP 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 preservatives should be established using the test for efficacy of antimicrobial preservation of the European Pharmacopoeia. 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 of 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 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.

Further details of in use testing for veterinary products is provided in the current CVMP Notes for Guidance on in use stability testing.

9. LABELLING

Labelling must be in accordance with relevant Community Directives - Council Directive 92/27/EEC and 81/851/EEC.

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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