PLASTIC PRIMARY PACKAGING MATERIALS

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Additional Notes This note for guidance concerns the application to plastic primary packaging materials of Part 2, sections A, C, and F of the Annex to Directive 75/318/EEC as amended, with a view to the granting of a marketing authorisation for a new medicinal product. The provisions of Community legislation relating to plastic materials intended to come into contact with foodstuffs, in particular Directive 90/218/EEC should be taken into account.

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PLASTIC PRIMARY PACKAGING MATERIALS

INTRODUCTION
This note for guidance is concerned with the application to plastic primary packaging materials of Part 2, sections A, C, F of the Annex to Directive 75/318/EEC as amended, with a view to the granting of a marketing authorisation for a new medicinal product.

The present note is limited to plastic primary (or immediate) packaging materials i.e. packaging materials intended to be in direct contact with the medicinal product. They comprise containers, closures, seals and other parts which come into contact with the medicinal product.

The data should be presented according to the standard format described in the Notice to Applicants (Volume II of The Rules governing Medicinal Products in the European Union), parts 2 A2, A4, C3 and F2.

Two other notes for guidance refer to containers: development pharmaceutics and process validation and stability tests on active substances and finished products.

The importance and characteristics of data to be given are related to the pharmaceutical dosage form (see appended summary).

When establishing the specifications for packaging materials for non-parenteral preparations, the provisions of Community legislation relating to plastic materials intended to come into contact with foodstuffs in particular Directive 90/128/EEC as amended, should be taken into account.

For packaging materials used for ophthalmic and parenteral products, appropriate development studies should be carried out if they are not described in the European Pharmacopoeia or in the pharmacopoeia of a Member State.

Reference should be made to monographs of the European Pharmacopoeia or of the national pharmacopoeia of a Member State.

PART 2 A.2 IMMEDIATE PACKAGING
This part of the dossier should contain a brief description of the container. It should include:
- the nature of the packaging material, indicating in particular the qualitative composition of its different parts and the non-plastic parts;
- a description of the closure (nature and method) including, if necessary, its watertight and airtight seal;
- a description of the method of opening and, if necessary, safety devices;
- information on the container (single or multidose) and dosing devices;
- a description of any tamper-evident closure and child resistant closure.
PART 2 A.4  DEVELOPMENT PHARMACEUTICS

A justification of the choice of the container should be given in relation to data on stability of
the active substance(s) and of the finished product, to the method of administration and to
any sterilisation procedures.

The data collected during the development should be presented to justify the choice of the
plastic material(s) and of the container(s). These data should include details on:
- tightness of closure
- protection of the contents against external factors.
- container/contents interaction (e.g. sorption, leaching)
- influence of the manufacturing process on the container (e.g. sterilisation conditions).

PART 2 C.3  PACKAGING MATERIAL (PRIMARY OR
IMMEDIATE PACKAGING)

3.1 Specifications and routine test

Information should be provided on:
- The construction of the container, with a list of the different components.
- The type of materials used in the different parts, and nature of polymers
- The specifications: the nature, the extent and the frequency of routine tests of
packaging materials vary significantly according to the type of material, the type of
immediate packaging and the use of the product. Due account should be taken of the
route of administration, e.g. for parenteral and ophthalmic products.

For example, the following tests may be performed:
- identification of plastic material
- visual inspection
- dimensional tests
- physical tests (as appropriate: e.g. tensile strength...)
- microbiological tests (as appropriate).

If the plastic material is not described in the European Pharmacopoeia or in the
pharmacopoeia of a Member State it is advisable to use another pharmacopoeia monograph as
a guide to establish the routine tests and the general methods of the pharmacopoeia to
establish the specifications. The tests and limits applied should be justified.

3.2 Scientific data

Scientific data collected during the development of the medicinal product concern the
following points: information as to the plastic itself and the plastic packaging material,
uniformity of the material used for packaging and interaction studies.
3.2.1. Information concerning the plastic material used for packaging pharmaceutical products

A. General information

The following information should be provided for plastic materials used in the container, including those already described in the pharmacopoeia where the monographs authorise the use of several additives from which the manufacturer may choose one or several (within certain limits).

- The name and grade given by the manufacturer of the material.
- For ophthalmic and parenteral preparations, the name of the plastic manufacturer.
- The chemical name of the material.
- The chemical name(s) of any monomer used.
- The complete qualitative composition of the plastic material is required where an interaction between the container and the contents occurs. The qualitative composition covers all substances, including additives such as antioxidants, stabilisers, catalysts, plasticisers, lubricants, solvents and/or dyes (comprising the colour index number and/or the EC number).

If the material has not been approved for use for packaging of food, toxicological data should be provided. In addition, toxicological information is required for plastics normally approved for use in food packaging, if they are used for parenteral or ophthalmic medicinal products.

B. Technical information

- Characteristics
  Description of the material, its solubility in various solvents.
- Identification of the material
  generally by infrared absorption spectrophotometry, with indication of the position of characteristic absorption bands. The infrared spectrum of the reference material should be provided: other methods of identification may be appropriate.
- Identification of the main additives
  in particular those which are likely to migrate into the contents (such as antioxidants, plasticisers, catalysts, initiators, etc.... and, for PVC, phthalates, adipates and organic tin compounds).
- Identification of dyes
  by using chromatographic or any other appropriate method.
- Tests
  • General tests
  • Mechanical tests
  • Physical tests: an extraction test should be performed where the plastic material is used as primary packaging material for liquid and semi-solid preparations.
The choice of solvent for this test depends on the composition of the product. The test should investigate the level of extractives (antioxidants, plasticisers...).

3.2.2 Container
The name of the manufacturer (also called converter) of the container should be specified for ophthalmic and parental preparations.

The converter should ensure that the manufacturing process is reproducible and that there is no change in the composition of the material as defined for the type-sample.

Any significant change in the composition of the plastic material needs new specifications and verification by the pharmaceutical manufacturer that the new packaging is suitable for the intended use.

PART 2 F.2 STABILITY - STUDIES OF MIGRATIONS AND INTERACTIONS

The choice of a packaging material is determined from studies concerning the protective effect of the packaging against various external influences and compatibility studies between the dosage form and the packaging.

The compatibility study forms part of the stability tests on the finished products and includes compatibility with synthetic elastomer closures.

A study scheme should be proposed, designed for each dosage form: solid forms, semi-solid forms and liquid forms.

Particular attention should be given to ophthalmic and parenteral preparations.

1. Dosage forms
1.1 Solid forms

For oral or topical solid dosage forms, the risk of migration is low and generally does not require a content/container interaction study. Solid forms intended for parenteral use may need interaction studies between the elastomer closure and the components of the formulation.

1.2 Semi-solid forms

The study should consist mainly of technological controls of the container and study of the eventual migration of additives or dyes. The risk of migration into aqueous or non-aqueous semi-solid requires suitable specific studies for each formulation.

The study should be performed under normal and accelerated conditions.

1.3 Liquid forms

The risks of migration require suitable specific studies for each formulation.

In the case of parenteral and ophthalmic products, determination of the active substance and preservative contents should be performed under simulated conditions of use.
Levels of extractives (e.g. antioxidants, plasticisers, catalysts processing aids etc....) should be investigated mainly for parenteral and ophthalmic products.

2. General scheme

2.1 Samples

During the development stage, migration studies on initial formulations often allow the choice of a suitable packaging material for the finished product to be chosen. The study should be performed on at least one batch of finished product.

2.2 Study condition

Studies should be performed under normal and accelerated conditions according to the current notes for guidance on stability.

2.3 Study methods

Simulation studies performed with extraction solvents (as in the case of food) can only be considered as predictive tests and do not preclude the need to perform a study on the finished product.

- Migration and interaction studies should include:
  - the control of technological characteristics for each pharmaceutical form.
  - a study on the leaching of antioxidants, mono- and oligomers, plasticisers, mineral compounds likely to migrate (e.g. calcium, barium, tin for PVC) and other additives according to the composition of the packaging material. Maximum limits may need to be proposed.
  - a study of the sorption of the formulation components to the packaging material.
## SUMMARY PRESENTATION OF THE DOCUMENTATION OF PLASTIC CONTAINERS AND PACKAGING MATERIAL

<table>
<thead>
<tr>
<th></th>
<th>Solid preparations</th>
<th>Semi-solid/liquid preparations</th>
<th>Ophthalmic and Parenteral preparations</th>
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<td><strong>including additives</strong></td>
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</table>

* Routine tests

** The studies of suitability toxicity and compatibility content-container and migrations are carried out during the development and not for routine test.