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**GUIDELINE ON
PLASTIC IMMEDIATE PACKAGING MATERIALS**

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This guideline replaces the Guideline on Plastic Primary Packaging Materials (Rules Governing Medicinal Products 3AQ10a).

Public

GUIDELINE ON PLASTIC IMMEDIATE PACKAGING MATERIALS

TABLE OF CONTENTS

1 INTRODUCTION 3

 1.1 Objective of the Guideline..... 3

 1.2 Scope of the Guideline 3

 1.3 General Principles..... 4

**2 LOCATION OF DOCUMENTATION TO BE PROVIDED IN THE MARKETING
AUTHORISATION APPLICATION 4**

3 DATA TO BE SUBMITTED..... 5

 3.1 General information..... 5

 3.2 Specifications..... 5

4 EXTRACTION STUDIES 6

5 INTERACTION STUDIES 6

 5.1 Migration Studies 7

 5.2 Sorption Studies..... 7

6 TOXICOLOGICAL INFORMATION/DOCUMENTATION..... 7

7 GLOSSARY 8

APPENDIX I: DECISION TREE ON THE PRESENTATION OF THE DOCUMENTATION 9

**APPENDIX II: DECISION TREE ON THE PRESENTATION OF THE DOCUMENTATION OF
PLASTIC PACKAGING MATERIAL 10**

APPENDIX III: CORRELATION TABLE FOR PRESENTING THE INFORMATION 11

GUIDELINE ON PLASTIC IMMEDIATE PACKAGING MATERIALS

1 INTRODUCTION

1.1 Objective of the Guideline

This Guideline supersedes the Guideline on Plastic Primary Packaging Materials published in the Rules Governing Medicinal Products 3AQ10a and addresses the information on plastic materials being used as immediate packaging for active substances and medicinal products to be submitted in marketing authorisation applications.

It concerns the application of Part 1, Module 3, sections 3.2.1.6, 3.2.2.2 and 3.2.2.7 of Annex I to Directive 2003/63/EC, amending Directive 2001/83/EC for human medicinal products, and Part 2, sections A, C and G of Annex 1 to Directive 2001/82/EC for veterinary medicinal products, respectively, to plastic immediate packaging materials.

1.2 Scope of the Guideline

The guideline covers the specific requirements for plastic immediate packaging materials. It is not intended to outline general requirements also applicable to other types of packaging materials or to properties of the container closure system, e.g. performance.

The guideline is limited to plastic immediate packaging materials, i.e. packaging materials intended to be in direct contact with the active substance or medicinal product. The materials may be part of the container, the closure or seal or of other parts of the container closure system(s). Elastomeres and natural and synthetic rubber are not within the scope of this guideline.

This guideline should not be applied retrospectively to already marketed products in their authorised packaging material. However, in new registration applications or in variation applications to introduce a new immediate plastic pack, plastic immediate packaging materials for active ingredients and medicinal products have to comply with the requirements outlined in this document, regardless whether the material is going to be used for the first time or has already been used for packaging of active substances or medicinal products.

1.3 General Principles

The data to be provided for plastic packaging materials depend on the physical state of the active substance (see decision tree in Appendix I) and the pharmaceutical dosage form and route of application of the medicinal product (see decision tree in Appendix II). The data should be presented according to the standard format described in the Notice to Applicants (Volume 2B of The Rules governing Medicinal Products in the European Union), CTD-Module 3, 3.2.S.6, 3.2.P.2.4 and 3.2.P.7, for human medicinal products or in the Notice to Applicants (Volume 6B of The Rules governing Medicinal Products in the European Union) Part 2 sections A, C and G, for veterinary medicinal products. A correlation table on the location of the EU-CTD dossier versus the previous version for human medicinal products (NTA, Vol. 2B, edition 1998) and the current version for veterinary medicinal products (NTA, Vol. 6B, edition 2004), respectively, is provided in Appendix III.

The guideline should be read in conjunction with the current versions of the guidelines on Development Pharmaceuticals (CPMP/QWP/155/96), Stability Testing: Stability Testing of New Drug Substances and Products (CPMP/ICH/2736/99) – Revision of CPMP/ICH/380/95 – and Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products (CPMP/QWP/122/02, corr.) for human medicinal products and the guidelines on Development Pharmaceuticals for Veterinary Medicinal Products (CVMP/315/98), Stability Testing of New Veterinary Drug Substances and Medicinal Products (CVMP/VICH/899/99) and Stability Testing of Existing Active Substances and Related Finished Products (CVMP/846/99) for veterinary medicinal products, respectively.

Furthermore, the provisions of Community legislation on plastic materials and objects in contact with foodstuffs, in particular Commission Directive 2002/72/EC relating to Plastic Materials and Articles intended to come into contact with foodstuffs, should be taken into account, when indicated in this guideline.

2 LOCATION OF DOCUMENTATION TO BE PROVIDED IN THE MARKETING AUTHORISATION APPLICATION

For ease of reading, reference regarding the location of information in the marketing authorisation application is only given for the CTD structure relevant to human medicinal products. Information on the location of information for veterinary products can be found in the correlation table provided in Appendix III.

Container Closure System for the Active Substance [3.2.S.6]

This part of the dossier should provide information on plastic materials used for container closure systems for active substances. This should include:

- general information on type and nature of the material according to section 3.1;
- specifications of the plastic material (see section 3.2)
- results of extraction and interaction studies, where necessary (see section 4 and 5), and/or toxicological documentation, where necessary (see section 6);

Development Pharmaceuticals [3.2.P.2.4]

The data collected during the development of a preparation should be presented to justify the choice of the plastic material(s) in relation to the stability, integrity and compatibility of the medicinal product, to the method of administration and to any sterilisation procedures, if applicable. The data should include details on

- the compatibility of the plastic material with the medicinal product by performing extraction and interaction studies, where appropriate (see section 4 and 5), and/or toxicological documentation, where applicable (see section 6).
- the photostability of the plastic material should be discussed if degradation products of the material caused by the impact of light may have a significant impact on the container/medicinal

- product compatibility
- the influence of the manufacturing process of the medicinal product on the plastic material, where applicable (e.g. sterilisation conditions).

Container Closure System for the Medicinal Product [3.2.P.7]

The information to be provided in this part of module 3 should include:

- a description of the container closure system, indicating all components of plastic material;
- general information on the plastic material selected for the component, as outlined in section 3.1 of this guideline.
- specifications for each plastic material, as outlined in section 3.2;

3 DATA TO BE SUBMITTED

3.1 General information

For all plastic materials that are used as immediate packaging material for actives substances or medicinal products

- the chemical name of the material
- the chemical name(s) of any monomer used

have to be indicated.

Further information is required where non-solid active substances or non-solid medicinal products are in contact with plastic materials as indicated below.

For plastic materials intended for packaging of non-solid active substances:

- the complete qualitative composition of the plastic material (including additives, such as antioxidants, stabilisers, plasticisers, lubricants, solvents and/or dyes) if the active substance packaging material is not described in the European Pharmacopoeia or in the pharmacopoeia of a Member State, and the supplier cannot certify compliance with foodstuff legislation.

For plastic materials used in packaging of non-solid medicinal products:

- the name of the material supplier, if the medicinal product is intended for inhalation, parenteral or ophthalmic administration
- the complete qualitative composition of the plastic material as listed above, if the medicinal product is intended for inhalation, parenteral or ophthalmic administration and the material is neither described in the European Pharmacopoeia, nor in the pharmacopoeia of a Member State or, additionally, in cases where the monograph authorises the use of several additives from which the manufacturer may choose one or several in defined limits. The qualitative composition should also be provided for non-compendial packaging materials used for non-solid medicinal products intended for oral and topical (except ophthalmic) administration, when the supplier cannot certify compliance with foodstuff legislation.

3.2 Specifications

When establishing the specifications of plastic packaging materials being in contact with active substances or medicinal products, reference should be made to the appropriate monographs of the European Pharmacopoeia or the monograph of the pharmacopoeia of a Member State. When referring to a monograph, compliance should be demonstrated.

If the plastic material is not described in the European Pharmacopoeia or in the pharmacopoeia of a Member State, an in-house monograph has to be established according to the list below, taking into account the general methods of the pharmacopoeia:

- description of the material.
- identification of the material
- characteristic properties, e.g. mechanical, physical parameters.

For plastic material intended for packaging of non-solid active substances and non-solid medicinal products, the in-house monograph should include further information, such as:

- identification of the main additives, in particular those which are likely to migrate into the contents (such as antioxidants, plasticisers, catalysts, initiators, etc.)
- identification of colorants
- the nature and amount of extractables, based on the results of the extraction studies (see section 4).

This information does not need to be part of the in-house specification if the plastic packaging material is used for non-solid medicinal products intended for oral or topical (except ophthalmic) administration, or for non-solid active substances where the supplier can certify compliance with the foodstuff legislation.

A certificate of analysis of one representative batch of the material should be provided to demonstrate compliance with the established in-house specification.

4 EXTRACTION STUDIES

The aim of extraction studies is to determine those additives of the material that might be extracted by the preparation or the active substance in contact with the material. Extraction studies are considered to be necessary for plastic material used for container closure systems of non-solid active substances and non-solid dosage forms for oral and topical (except ophthalmic) use if the material is neither described in the European Pharmacopoeia nor in the pharmacopoeia of a Member State, nor has been approved for foodstuff packaging. For non-compendial plastic material used for container closure systems for non-solid medicinal products intended for inhalation, parenteral or ophthalmic administration, extraction studies are required even when approved for use in food packaging.

The studies typically involve exposing a sample of the material to an appropriate solvent system under stress conditions to increase the rate of extraction. The solvent used for extraction should have the same propensity to extract substances as the active substance/dosage form as appropriate. In the case of medicinal products the preferred solvent would be the medicinal product or placebo vehicle. The nature and amount of the extracted substances should be listed in the specification of the packaging material.

5 INTERACTION STUDIES

In order to evaluate the suitability of the selected plastic packaging material for the intended use, the compatibility of the material with the active substance or the medicinal product should be demonstrated. Testing may be performed by use of the plastic material or the plastic component or the container itself. The extent and design of interaction studies depend on the physical state of the active substance and the dosage form of the medicinal product, respectively:

For solid active substances and solid dosage forms: the risk of interaction is low and generally does not require a content/container interaction study. Solid dosage forms intended for inhalation or parenteral use, e.g. lyophilised products, may need interaction studies between the packaging material and the components of the formulation.

For non-solid active substances and liquid dosage forms: the risk of interaction requires comprehensive and suitable studies specific for each active substance/formulation. The studies should evaluate the critical functional characteristics of the container/delivery system and should ensure that no significant alterations occur leading to a lesser quality of the active substance or the medicinal product.

Interaction studies may include migration studies to monitor the leaching of substances from the plastic material into the formulation/active substance and/or sorption studies to evaluate a possible loss

of drug quality due to adsorption or absorption effects.

5.1 Migration Studies

During the development stage, migration studies should be performed on the active substance/initial formulation to allow the choice of a suitable packaging material for the active substance and the medicinal product, respectively.

Migration studies during development are necessary when extraction studies have resulted in one or several extractables (see section 4). In these situations, it should be demonstrated that in conditions representative for the intended use, substances will not migrate in such quantities as to alter the efficacy and stability of the active substance/medicinal product or to present a toxicological risk. Tests should be performed on at least one batch of the active substance/medicinal product, as appropriate. Simulation studies performed with test media (as in the case of food) can only be considered as preliminary tests and do not preclude the need to perform studies on the active substance/medicinal product itself. The analytical methods should be described, taking into account the general methods of the pharmacopoeia. Non-compendial analytical methods are to be validated. Maximum limits for leachables may need to be proposed.

Migration studies may only be omitted if, based on the outcome of the extraction studies, the calculated maximum amount of individual leachable substance that may be present in the active substance/medicinal product leads to levels demonstrated to be toxicologically safe. When a migration study is not considered necessary and thus is not conducted, a justification should be provided.

If the plastic material is composed of layers of different plastic materials, the possibility of migration of components of the external layers into the medicinal product should be evaluated, depending on the nature of the product and its intended use. Furthermore, it should be demonstrated that no components of ink or adhesives applied to the outer surface of the container/closure system will migrate into the medicinal product.

In those cases, where no developmental migration studies have been performed, leachables should be monitored during formal stability studies conducted under normal and accelerated storage conditions.

5.2 Sorption Studies

Developmental studies may be necessary to investigate interactions between the packaging material and the formulation due to sorption of the active substance or an excipient to the packaging material, leading to changes in product quality. Sorption studies have to be performed when changes in the stability of the medicinal product are observed during the stability studies which may be effected by adsorption or absorption of formulation components to the plastic packaging.

Sorption studies for plastic materials intended for packaging of non-solid active substances are not considered to be necessary.

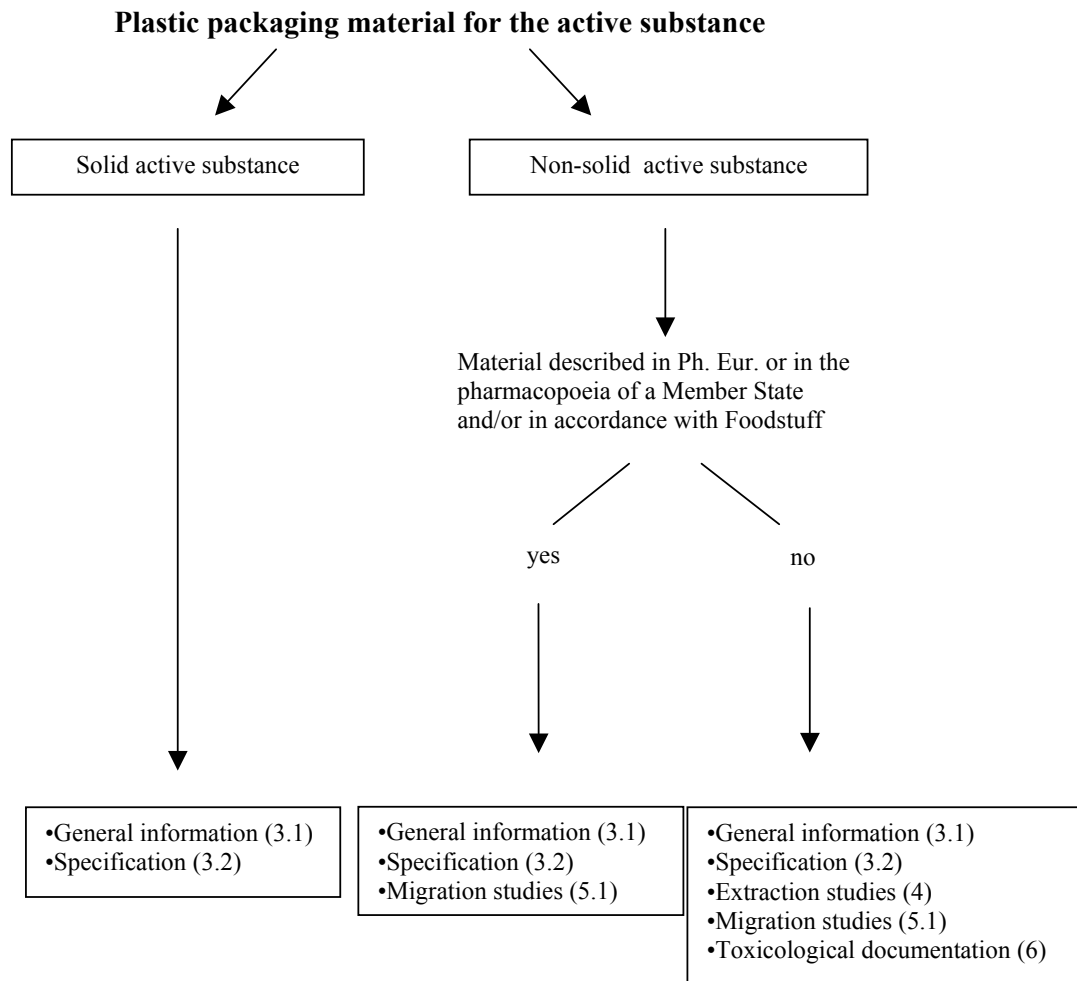
6 TOXICOLOGICAL INFORMATION/DOCUMENTATION

For plastic material used for container closure systems for active substances or medicinal products, toxicological data should be provided for extractables and leachables, depending on their level and chemical structure. If the plastic material or additives used are described in the European Pharmacopoeia, the pharmacopoeia of a Member state or have been approved for use in food packaging, toxicological data may not be required. For non-compendial plastic materials and additives used for container closure systems of medicinal products intended for inhalation, parenteral or ophthalmic administration, toxicological information is required even when approved for use in food packaging.

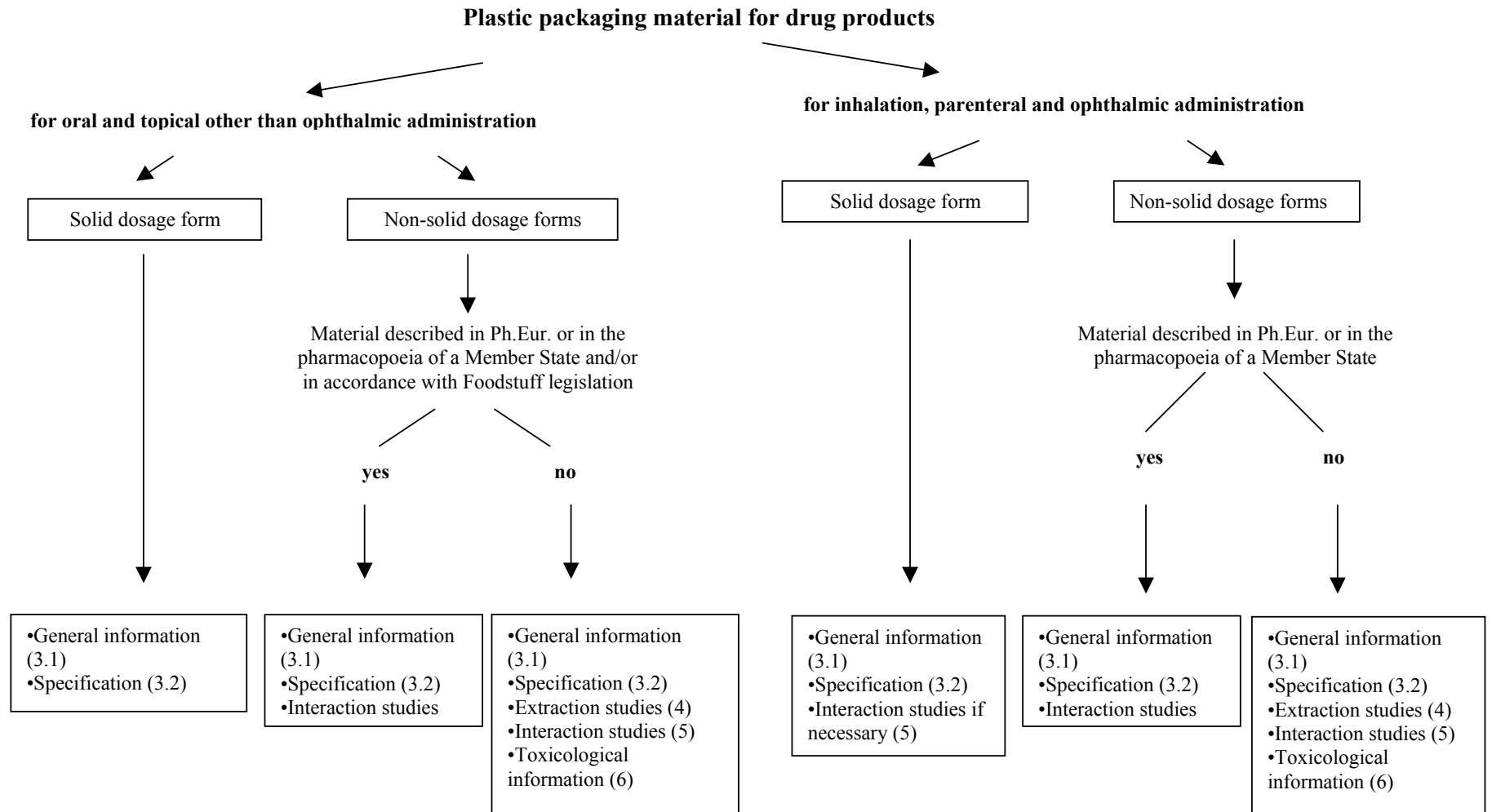
7 GLOSSARY

Compatibility:	proof that no serious interaction between container closure material and content occurs that leads to altering efficacy and stability of the product or that presents a risk of toxicity.
Container closure system	the sum of packaging components that together contain and protect the active substance or the dosage form. This includes immediate packaging components and secondary packaging components, if the latter are intended to provide additional protection to the active substance or to the drug product.
Extraction studies:	testing that specifically involves exposing a sample of the component to an appropriate solvent system at extreme conditions in order to maximise the amount of extractables from the packaging in the solvent.
Interaction studies:	studies to detect any effects between plastic packaging component and product leading to unacceptable changes in the quality of the product or the packaging under normal storage/use conditions.
Migration:	release of substances (leachables) from the plastic component into the content of the container under conditions which reproduce those of the intended use.
Packaging component:	any single part of a container closure system including containers (e.g. ampoules, vials, bottles), closures (e.g. screw caps, stoppers), stopper overseals, container inner seals, administration accessories and container labels.
Plastic material:	a material that contains one or more organic macromolecular compounds obtained by polymerisation, polycondensation or polyaddition or any other similar process from molecules with a lower weight or by chemical alteration of natural macromolecules as an essential ingredient. Elastomeres and natural and synthetic rubber are not within the scope of this guideline.
Sorption:	bonding of a solute to a plastic packaging component as a physicochemical phenomenon related to the properties of the packaging material and the chemical properties of the active substance or other soluble substances in the preparation.
Specification:	a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria as appropriate for the tests described.
Suitability:	assessment of the container closure system in regard to protection, safety, compatibility and performance (function).

8 **APPENDIX I: DECISION TREE ON THE PRESENTATION OF THE DOCUMENTATION**



9 APPENDIX II: DECISION TREE ON THE PRESENTATION OF THE DOCUMENTATION OF PLASTIC PACKAGING MATERIAL



10 APPENDIX III: CORRELATION TABLE FOR PRESENTING THE INFORMATION

Information	Medicinal products for human use		Medicinal products for veterinary use
	NTA Vol. 2B, edition 2003 EU-CTD	NTA Vol. 2B, edition 1998 (old version)	NTA Vol. 6B, edition 2004
Container closure system for active substances	3.2.S.6	/	/
Container closure system for medicinal products	3.2.P.2.4	Part II A4	Part 2 A4
	3.2.P.7	Part II C3	Part 2 G