

[<sup>F1</sup>ANNEX IANALYTICAL, PHARMACOTOXICOLOGICAL AND CLINICAL STANDARDS  
AND PROTOCOLS IN RESPECT OF THE TESTING OF MEDICINAL PRODUCTS**Textual Amendments**

- F1** Substituted by [Commission directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use \(Text with EEA relevance\)](#).

## PART III

**PARTICULAR MEDICINAL PRODUCTS**

## 1. BIOLOGICAL MEDICINAL PRODUCTS

## 1.1. Plasma-derived medicinal product

For medicinal products derived from human blood or plasma and by derogation from the provisions of Module 3, the dossier requirements mentioned in ‘Information related to the starting and raw materials’, for starting materials made of human blood/plasma may be replaced by a Plasma Master File certified in accordance with this Part.

## a) Principles

For the purposes of this Annex:

- Plasma Master File shall mean a stand-alone documentation, which is separate from the dossier for marketing authorisation which provides all relevant detailed information on the characteristics of the entire human plasma used as a starting material and/or a raw material for the manufacture of sub/intermediate fractions, constituents of the excipient and active substance(s), which are part of medicinal products or medical devices referred to in Directive 2000/70/EC of the European Parliament and of the Council of 16 November 2000 amending Council Directive 93/42/EC as regards medical devices incorporating stable derivatives of human blood or human plasma<sup>(1)</sup>.
- Every centre or establishment for fractionation/processing of human plasma shall prepare and keep updated the set of detailed relevant information referred to in the Plasma Master File.
- The Plasma Master File shall be submitted to the Agency or to the competent authority by the applicant for a marketing authorisation or the holder of the marketing authorisation. Where the applicant for a marketing authorisation or the marketing authorisation holder differs from the holder of the Plasma Master File, the Plasma Master File shall be made available to the applicant or marketing authorisation holder for submission to the competent authority. In any case, the applicant or marketing authorisation holder shall take responsibility for the medicinal product.
- The competent authority that is evaluating the marketing authorisation shall await for the Agency to issue the certificate before deciding on the application.
- Any marketing authorisation dossier containing a human plasma-derived constituent shall refer to the Plasma Master File corresponding to the plasma used as a starting/raw material.

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b) Content

In accordance with the provisions of Article 109, as amended by Directive 2002/98/EC, which refers to the requirements for donors and the testing of donations, the Plasma Master File shall include information on the plasma used as starting/raw material, in particular:

- (1) Plasma origin
  - (i) information on centres or establishments in which blood/plasma collection is carried out, including inspection and approval, and epidemiological data on blood transmissible infections.
  - (ii) information on centres or establishments in which testing of donations and plasma pools is carried out, including inspection and approval status.
  - (iii) selection/exclusion criteria for blood/plasma donors.
  - (iv) system in place which enables the path taken by each donation to be traced from the blood/plasma collection establishment through to finished products and vice versa.
- (2) Plasma quality and safety
  - (i) compliance with European Pharmacopoeia Monographs.
  - (ii) testing of blood/plasma donations and pools for infectious agents, including information on test methods and, in the case of plasma pools, validation data on the tests used.
  - (iii) technical characteristics of bags for blood and plasma collection, including information on anticoagulants solutions used.
  - (iv) conditions of storage and transport of plasma.
  - (v) procedures for any inventory hold and/or quarantine period.
  - (vi) characterisation of the plasma pool.
- (3) System in place between the plasma-derived medicinal product manufacturer and/or plasma fractionator/processor on the one hand, and blood/plasma collection and testing centres or establishments on the other hand, which defines the conditions of their interaction and their agreed specifications.

In addition, the Plasma Master File shall provide a list of the medicinal products for which the Plasma Master File is valid, whether the medicinal products have been granted a marketing authorisation or are in the process of being granted such an authorisation, including medicinal products referred to in Article 2 of Directive 2001/20/EC of the European Parliament and of the Council relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

c) Evaluation and Certification

- For medicinal products not yet authorised, the marketing authorisation applicant shall submit a full dossier to a competent authority, which shall be accompanied by a separate Plasma Master File where one does not already exist.
- The Plasma Master File is subject to a scientific and technical evaluation carried out by the Agency. A positive evaluation shall result in a certificate of compliance with

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Community legislation for the Plasma Master File, which shall be accompanied by the evaluation report. The certificate issued shall apply throughout the Community.

- The Plasma Master File shall be updated and re-certified on an annual basis.
- Changes subsequently introduced to the terms of a Plasma Master File must follow evaluation procedure laid down by Commission Regulation (EC) No 542/95<sup>(2)</sup> concerning the examination of variations to the terms of a marketing authorisation falling within the scope of Council regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products<sup>(3)</sup>. Conditions for the assessment of these changes are laid down by Regulation (EC) No 1085/2003.
- As a second step to the provisions in the first, second, third and fourth indents, the competent authority that will grant or has granted the marketing authorisation shall take into account the certification, re-certification or variation of the Plasma Master File on the concerned medicinal product(s).
- By derogation from the provisions of the second indent of the present point (evaluation and certification), where a Plasma Master File corresponds only to blood/plasma-derived medicinal products the marketing authorisation of which is restricted to a single Member State, the scientific and technical evaluation of the said Plasma Master File shall be carried out by the national competent authority of that Member State.

## 1.2. Vaccines

For vaccines for human use and by derogation from the provisions of Module 3 on ‘Active substance(s)’, the following requirements when based on the use of a Vaccine Antigen Master File system shall apply.

The marketing authorisation application dossier of a vaccine other than human influenza vaccine, shall be required to include a Vaccine Antigen Master File for every vaccine antigen that is an active substance of this vaccine.

### a) Principles

For the purposes of this Annex:

- Vaccine Antigen Master File shall mean a stand-alone part of the marketing authorisation application dossier for a vaccine, which contains all relevant information of biological, pharmaceutical and chemical nature concerning each of the active substances, which are part of this medicinal product. The stand-alone part may be common to one or more monovalent and/or combined vaccines presented by the same applicant or marketing authorisation holder.
- A vaccine may contain one or several distinct vaccine antigens. There are as many active substance(s) as vaccine antigen(s) present in a vaccine.
- A combined vaccine contains at least two distinct vaccine antigens aimed at preventing a single or several infectious diseases.
- A monovalent vaccine is a vaccine, which contains one vaccine antigen aimed at preventing a single infectious disease.

### b) Content

The Vaccine Antigen Master File shall contain the following information extracted from the relevant part (Active substance) of Module 3 on ‘Quality Data’ as delineated in Part I of this Annex:

Active Substance

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1. General Information, including compliance with the relevant monograph(s) of the European Pharmacopoeia.
  2. Information on the manufacture of the active substance: this heading must cover the manufacturing process, information on the starting and raw materials, specific measures on TSEs and adventitious agents safety evaluation and facilities and equipment.
  3. Characterisation of the active substance
  4. Quality control of the active substance
  5. Reference standard and materials
  6. Container and closure system of the active substance
  7. Stability of the active substance.
- c) Evaluation and Certification
- For novel vaccines, which contain a novel vaccine antigen, the applicant shall submit to a competent authority a full marketing-authorisation application dossier including all the Vaccine Antigen Master Files corresponding to each single vaccine antigen that is part of the novel vaccine where no master file already exists for the single vaccine antigen. A scientific and technical evaluation of each Vaccine Antigen Master File shall be carried out by the Agency. A positive evaluation shall result in a certificate of compliance to the European legislation for each Vaccine Antigen Master File, which shall be accompanied by the evaluation report. The certificate shall apply throughout the Community.
  - The provisions of the first indent shall also apply to every vaccine, which consists of a novel combination of vaccine antigens, irrespective of whether or not one or more of these vaccine antigens are part of vaccines already authorised in the Community.
  - Changes to the content of a Vaccine Antigen Master File for a vaccine authorised in the Community shall be subject to a scientific and technical evaluation carried out by the Agency in accordance with the procedure laid down in Commission Regulation (EC) No 1085/2003. In the case of a positive evaluation the Agency shall issue a certificate of compliance with Community legislation for the Vaccine Antigen Master File. The certificate issued shall apply throughout the Community.
  - By derogation from the provisions of the first, second and third indents of the present point (evaluation and certification), where a Vaccine Antigen Master File corresponds only to a vaccine which is the subject of a marketing authorisation which has not been/will not be granted according to a Community procedure, and, provided the authorised vaccine includes vaccine antigens which have not been evaluated through a Community procedure, the scientific and technical evaluation of the said Vaccine Antigen Master File and its subsequent changes, shall be carried out by the national competent authority that has granted the marketing authorisation.
  - As a second step to the provisions in the first, second, third and fourth indents, the competent authority that will grant or has granted the marketing authorisation shall take into account the certification, re-certification or variation of the Vaccine Antigen Master File on the concerned medicinal product(s).]

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- (1) [<sup>F1</sup>OJ L 313, 13.12.2000, p. 22.]
- (2) [<sup>F1</sup>OJ L 55, 11.3.1995, p. 15.]
- (3) [<sup>F1</sup>OJ L 214, 24.8.1993, p. 1.]

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