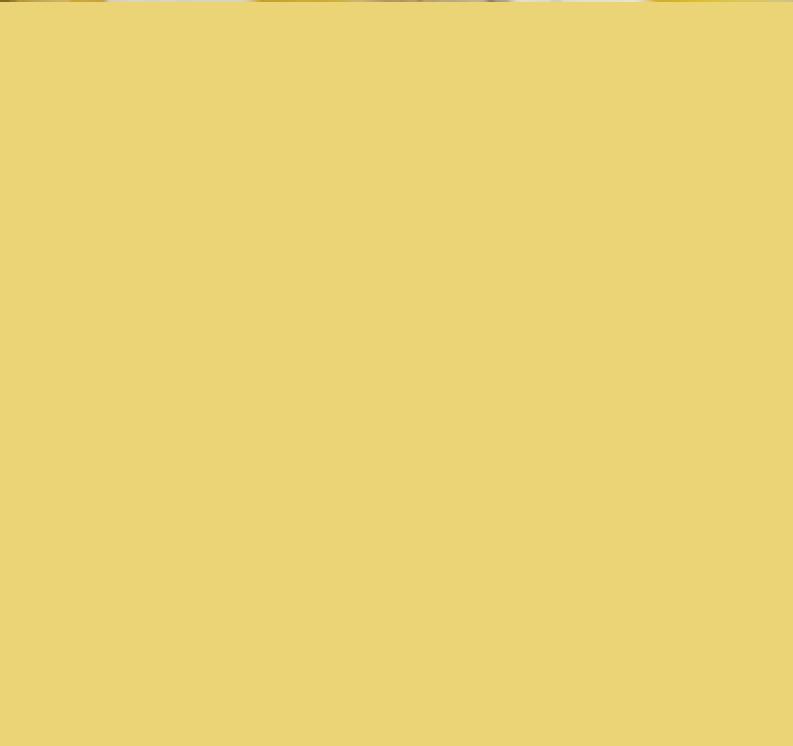




Technical guide for the **ELABORATION AND USE OF MONOGRAPHS ON HUMAN PLASMA- DERIVED PRODUCTS**



European Pharmacopoeia

EDQM
2015

Technical guide for the

**ELABORATION AND USE OF
MONOGRAPHS AND GENERAL
CHAPTERS ON HUMAN PLASMA
DERIVED PRODUCTS**

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**Technical guide for the elaboration and use of
monographs and general chapters on human
plasma-derived products**

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1. PURPOSE OF THE GUIDE

This document is intended to provide guidance to authors (and contributors) and users of European Pharmacopoeia monographs and general chapters on medicinal products derived from human blood and human plasma (hereinafter called "plasma-derived products"). This applies in particular to:

1. Group of Experts No. 6B (Human blood and blood products)
2. Authorities responsible for granting marketing authorisations for plasma-derived products,
3. Official Medicines Control Laboratories (OMCLs),
4. Manufacturers of plasma-derived products,
5. Public and private analytical laboratories working for one of the above,
6. The Secretariat of the European Pharmacopoeia and other departments of the European Directorate for the Quality of Medicines & HealthCare (EDQM).

2. STATUS AND SCOPE OF THE GUIDE

The monographs and general chapters of the European Pharmacopoeia set out the official standards for medicinal products. This guide provides information on the elaboration and use of these standards but has no official status. In the event of doubt or dispute, the text of the European Pharmacopoeia alone is authoritative.

3. GENERAL INFORMATION

3.1 PHARMACOPOEIAL REQUIREMENTS

Monographs and general chapters of the European Pharmacopoeia must be interpreted with reference to the *General Notices* of the European Pharmacopoeia. All users of the European Pharmacopoeia must be familiar with these notices. The main items relevant for plasma-derived products are given below:

Statements in monographs are mandatory requirements unless otherwise stated: *“Unless otherwise indicated in the General Notices or in the monographs, statements in monographs constitute mandatory requirements. General chapters become mandatory when referred to in a monograph; unless such reference is made in a way that indicates that it is not the intention to make the text referred to mandatory but rather to cite it for information.”* (Ph. Eur. 8th Edition)

As regards demonstration of compliance with the European Pharmacopoeia, the *General Notices* state that:

“(1) An article [that is the subject of a monograph] is not of Pharmacopoeia quality unless it complies with all the requirements stated in the monograph. This does not imply that performance of all the tests in a monograph is necessarily a prerequisite for a manufacturer in assessing compliance with the Pharmacopoeia before release of a product. The manufacturer may obtain assurance that a product is of Pharmacopoeia quality on the basis of its design, together with its control strategy and data derived, for example, from validation studies of the manufacturing process.

(2) An enhanced approach to quality control could utilise process analytical technology (PAT) and/or real-time release testing (including parametric release) strategies as alternatives to end-product testing alone. Real-time release testing in circumstances deemed appropriate by the competent authority is thus not precluded by the need to comply with the Pharmacopoeia.” (Ph. Eur. 8th Edition)

As regards the use of alternative methods of analysis, the *General Notices* state that: *“The tests and assays described are the official methods upon which the standards of the Pharmacopoeia are based. With the agreement of the competent authority, alternative methods of analysis may be used for control purposes, provided that the methods used enable an unequivocal decision to be made as to whether compliance with the standards of the monographs would be achieved if the official methods were used. In the event of doubt or dispute, the methods of analysis of the Pharmacopoeia are alone authoritative.” (Ph. Eur. 8th Edition)*

3.2 ALTERNATIVE METHODS

The test methods prescribed in monographs and general chapters are the reference methods on which the quality standards are based. As indicated above, under 3.1 Pharmacopoeial requirements, alternative methods of analysis may be used when appropriate. Pharmacopoeial methods have been chosen for application to all relevant products that were available at the time of method elaboration. In accordance with the *General Notices*, other available methods may be used if it is demonstrated by validation that the alternative method is at least equivalent to the official method. Although the pharmacopoeial methods have been developed for application in a variety of laboratories with standard equipment, this does not rule out the use of alternative, validated methods.

Monographs and general chapters are revised periodically to keep pace with progress in analytical techniques but pending these revisions new methods may be used as alternatives, if suitably validated and the use is authorised by the competent authority.

Use of animals for scientific purposes

In accordance with the provisions of the *European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (1986)*¹ with consideration of the EU Directive 2010/63/EU², European Pharmacopoeia tests must be carried out in such a way as to use the minimum number of animals for a significant result and to cause the least pain, suffering, distress or lasting harm. Humane endpoints must be used wherever possible for all tests, even if not referred to in a specific monograph since references to humane endpoints are included as examples only where practical advice can be given.

Additionally, as stated in the *General Notices*, in demonstrating compliance with the European Pharmacopoeia, manufacturers may consider establishing additional systems to monitor consistency of production. With the agreement of the competent authority, the choice of tests performed to assess compliance with the Pharmacopoeia when animal tests are prescribed is established in such a way that animal usage is minimised as much as possible.

3.3 MONOGRAPHS AND GENERAL CHAPTERS

Monographs on plasma-derived products are published in the European Pharmacopoeia in alphabetical order of the title.

The following general chapters published under headings 2.6. *Biological tests* and 2.7. *Biological assays* apply whenever they are given as a reference in a monograph on a plasma-derived product:

Biological tests specific to plasma-derived products:

- Prekallikrein activator (2.6.15)
- Test for anticomplementary activity of immunoglobulin (2.6.17)
- Anti-A and anti-B haemagglutinins (2.6.20)
- Activated coagulation factors (2.6.22)
- Test for anti-D antibodies in human immunoglobulin (2.6.26)
- Test for Fc function of immunoglobulin (2.7.9)

Biological assays specific to plasma-derived products:

- Assay of human coagulation factor VIII (2.7.4)
- Assay of human coagulation factor VII (2.7.10)

¹ European convention for the protection of vertebrate animals used for experimental and other scientific purposes. European Treaty series No. 123. Council of Europe (1986).² DIRECTIVE 2010/63/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 22 September 2010 on the protection of animals used for scientific purposes.³ www.edqm.eu/hd

² DIRECTIVE 2010/63/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 22 September 2010 on the protection of animals used for scientific purposes.³ www.edqm.eu/hd

- Assay of human coagulation factor IX (2.7.11)
- Assay of heparin in coagulation factors (2.7.12)
- Assay of human anti-D immunoglobulin (2.7.13)
- Assay of human antithrombin III (2.7.17)
- Assay of human coagulation factor II (2.7.18)
- Assay of human coagulation factor X (2.7.19)
- Assay of human von Willebrand factor (2.7.21)
- Assay of human coagulation factor XI (2.7.22)
- Assay of human plasmin inhibitor (2.7.25)
- Assay of human protein C (2.7.30)
- Assay of human protein S (2.7.31)
- Assay of human α -1-proteinase inhibitor (2.7.32)
- Assay of human C1-esterase inhibitor (2.7.34)

Additional tests not restricted to plasma-derived products:

- Sterility (2.6.1),
- Pyrogens (2.6.8)
- Bacterial Endotoxins (2.6.14)
- Monocyte-Activation Test (2.6.30)
- Nucleic acid amplification techniques (2.6.21): *Validation of nucleic acid amplification techniques (NAT) for the detection of hepatitis C virus (HCV) RNA in plasma pools : guidelines and Validation of nucleic acid amplification techniques (NAT) for quantification of B19 Virus (B19V) DNA in plasma pools: guidelines*
- Serological testing

3.4. HOW MONOGRAPHS AND GENERAL CHAPTERS ARE ELABORATED AND UPDATED

3.4.1. Inclusion of a new monograph or a new general chapter in the European Pharmacopoeia

Proposals to add a new monograph or new general chapter to the European Pharmacopoeia work programme can be made by:

- the Chair of the European Pharmacopoeia Commission;
- a delegation to the European Pharmacopoeia Commission;
- the Chair of Group 6B;
- the Secretariat of the European Pharmacopoeia for example on the basis of information and data provided via the *EDQM Helpdesk*³ by a manufacturer or by a user of the European Pharmacopoeia.

The European Pharmacopoeia Commission takes a decision to accept or refuse the proposal for a new monograph or new general chapter. If accepted, the elaboration of the new monograph or general chapter is added to the work programme of the Group of experts (see the *Rules of procedure of the European Pharmacopoeia Commission*⁴).

For many classes of medicinal substances or products, monographs or general chapters are usually (but not always) included in the European Pharmacopoeia only when the medicinal substance or product is produced by more than one manufacturer. This limitation is not always applied since it has been found that there can be a need for an official European Pharmacopoeia standard even when there is only one manufacturer of a substance or product.

The quality standards attained by the products that are already on the market are taken into consideration during the elaboration of a new monograph or general chapter. Consequently, where there is sufficient information demonstrating that the product is of pharmacopoeial quality, it will not be necessary to retest these products to show compliance with the pharmacopoeial requirements when the monograph or general chapter is finalised and published in the European Pharmacopoeia.

Once the new monograph or general chapter is drafted, it is published in *Pharmeuropa* for public enquiry. Interested parties have 3 months to send their comments to their National Pharmacopoeial Authority (NPA), which collates all the comments from that country. NPAs then have 2 months to send the compiled comments to the Secretariat of the European Pharmacopoeia via the *EDQM Document Review Tool (DRT)*⁵. Manufacturers outside Europe and pan-European organisations have 3 months to send their comments to the Secretariat via the *Helpdesk*⁶.

The Secretariat consolidates the submitted comments which are then examined by Group 6B following the end of the consultation period.

³ www.edqm.eu/hd

⁴ Rules of Procedure of the European Pharmacopoeia Commission. _PA/PH/SG (11) 53 DEF. Council of Europe, European Directorate for the Quality of Medicines & HealthCare (2011).

⁵ <http://drt.edqm.eu/>

⁶ www.edqm.eu/hd

After review of these comments, if there are no major changes made to the monograph or general chapter published for comment in *Pharmeuropa*, the monograph or general chapter is proposed for adoption at the next European Pharmacopoeia Commission session. If a major change is made to the monograph or general chapter, it is again published for public enquiry in *Pharmeuropa*.

When the monograph or general chapter is adopted, it is published in the European Pharmacopoeia 6 months after the Commission session at which it was adopted, and implemented 6 months later. If the monograph or general chapter is not adopted by the European Pharmacopoeia Commission, either it returns to the Group for further elaboration or no monograph or general chapter on the particular product or method is published in the European Pharmacopoeia.

3.4.2. Revision of monographs and general chapters for plasma-derived products

Proposals to revise a text can be made by:

- the Chair of the European Pharmacopoeia Commission;
- a delegation; to the European Pharmacopoeia Commission;
- the Chair of Group 6B;
- the Secretariat of the European Pharmacopoeia, for example on the basis of information and data provided via the *EDQM Helpdesk*⁷ by a manufacturer or by a user of the European Pharmacopoeia.

The European Pharmacopoeia Commission refers requests for revision to the relevant Group of Experts (see the *Rules of Procedure of the European Pharmacopoeia Commission*⁸).

A request for revision must be submitted with a justification for this revision, supported by relevant data and information.

During the revision of a monograph or general chapter, the standards attained by plasma-derived products that are already on the market are taken into consideration.

Once the monograph or general chapter is revised, it is published in *Pharmeuropa* for public enquiry. Interested parties have 3 months to submit their comments to their NPA, which consolidates all the comments from that country. NPAs then have 2 months to send the compiled comments to the Secretariat of the European Pharmacopoeia via the *EDQM Document Review Tool (DRT)*⁹. Manufacturers outside Europe and pan-European organisations have 3 months to send their comments to the Secretariat of the European Pharmacopoeia via the *Helpdesk*¹⁰. The Secretariat consolidates the submitted comments which are then examined by Group 6B following the end of the consultation period.

After review of these comments, if there are no major changes to the monograph or general chapter published for comment in *Pharmeuropa*, it is proposed for adoption at the next

⁷ www.edqm.eu/hd

⁸ Rules of Procedure of the European Pharmacopoeia Commission. _PA/PH/SG (11) 53 DEF. Council of Europe, European Directorate for the Quality of Medicines & HealthCare (2011).

⁹ <http://drt.edqm.eu/>

¹⁰ www.edqm.eu/hd

European Pharmacopoeia Commission session. If a major change is made to the monograph or general chapter, it is again published for public enquiry in *Pharmeuropa*.

When the revised monograph or general chapter is adopted, it is published in the European Pharmacopoeia 6 months after the Commission session at which it was adopted, and implemented 6 months later. If the revised monograph or general chapter is not adopted by the European Pharmacopoeia Commission, either it returns to the Group for further elaboration or it remains as previously published.

4. CONTENT OF MONOGRAPHS

4.1. STRUCTURE AND CONTENT OF MONOGRAPHS FOR *PLASMA-DERIVED PRODUCTS*

4.1.1. General points

The pharmacopoeial requirements for plasma-derived products and the tests to be carried out are those described in the relevant specific monograph, where one exists.

The provisions of the class-specific monographs *Human plasma for fractionation (0853)*, *Human normal immunoglobulin for intramuscular administration (0338)*, *Human normal immunoglobulin for subcutaneous administration (2788)* and *Human normal immunoglobulin for intravenous administration (0918)* apply to all fractionated products, human normal specific immunoglobulins for intramuscular administration, subcutaneous administration and intravenous administration, respectively, including those for which there is no individual specific monograph. These class-specific monographs prescribe essential requirements which supplement and expand on requirements contained in the monographs for specific substances or products. The authors and users of specific monographs must be familiar with the contents of the relevant class-specific monograph in order to be able to draft or use the specific monographs correctly.

The requirements given in the class-specific monographs are usually not repeated in the specific monographs. The specific monographs include a reference to the class-specific monograph.

The specific monographs must be used and applied, taking account of the explanations, guidance and requirements given in the *General Notices*, general monographs and the class-specific monographs for fractionated products mentioned above.

It is expected that the tests and assay methods used routinely are appropriately transferred and checked for suitability by the users, in accordance with accepted procedures, e.g. those in the Technical Guide for the Elaboration of Monographs of the European Pharmacopoeia.

The monographs are regularly updated to be in line with the guidelines established by European Medicines Agency (EMA) on plasma derived products¹¹ such as the core Summary of Product Characteristics.

4.1.2. Monograph sections

The various sections contained in the monographs are mandatory, with the exception of the *Storage* section and for some substances or products, the *Labelling* section.

Statements provided for information are identified by their content and drafting style. See also the *General Notices* (Ph. Eur. 8th Edition).

DEFINITION

This section defines the scope of the monograph and its applicability to products on the market. The composition of the product is briefly stated.

It states:

- the physical status of the preparation (liquid or freeze-dried);
- the route of administration (for immunoglobulins);
- the source of the active substance (normally: human plasma for fractionation);
- the main (active) protein component(s);
- a description of the active substance (if applicable);
- other possible active substances usually associated with the intended active substance;
- possible contaminating active substances (e.g. IgA in immunoglobulins or activated coagulation factors in factor preparations);
- other ingredients (e.g. heparins);
- the potency or specific biological activity, whichever applicable;
- for specific immunoglobulin: exceptions from and/or additions to the requirements for normal immunoglobulin preparations for intramuscular, subcutaneous or intravenous administration.

Allowed substances are included in the *Definition* section. By default, should a substance or class of auxiliary substances (excipients, stabilisers, other ingredients, etc.) not be

¹¹

http://www.ema.europa.eu:80/ema/index.jsp?curl=pages/regulation/general/general_content_000082.jsp&mid=WC0b01ac0580027547 and
http://www.ema.europa.eu:80/ema/index.jsp?curl=pages/regulation/general/general_content_000388.jsp&mid=WC0b01ac0580032ec8

mentioned in the *Definition* section, it is prohibited. Prohibited substances are included in the Production section.

The monograph sets the official standard for all products covered by this definition.

If a new plasma-derived product is developed with an active substance covered by a specific monograph but of a new type, which falls outside the existing monograph, this may lead to revision of the monograph or elaboration of a new one. If a product is not covered by the scope of a specific monograph, the monograph is not applicable to this product. In this case, only the class-specific monographs apply.

PRODUCTION

This section describes essential features of the manufacturing process, up to and including batch release, and with development/validation tests that may be carried out in-process or on the final lot conducted to provide assurance that the product is of Pharmacopoeia quality (where not applied as routine batch test).

This section is primarily addressed to manufacturers. Apart from the monograph on *Human plasma for fractionation (0853)*, monographs on plasma-derived products in the European Pharmacopoeia cover substances or products prepared industrially in batches. Preparations produced in blood banks/transfusion centres (e.g. red cell concentrates, fresh frozen plasma) are not covered by the European Pharmacopoeia. Nevertheless, the principles described in the *EDQM Guide to the preparation, use and quality assurance of blood components* (current edition¹²) for donor selection and blood collection shall be considered.

The Production section contains appropriate details on the production method, including aseptic filling and freeze-drying, where applicable. In addition, standard sentences are added to ensure that production steps include but are not limited to (only general cases are detailed below):

- procedures to maintain functional integrity of the substance;
- procedures designed to minimise activation of coagulation factors, where applicable;
- procedures designed to remove, inactivate and control agents of infection;
- procedures for validation of removal of auxiliary substances;
- procedures for validation of lot-to-lot consistency that are not verified on the final lot;
- prohibition of the use of antimicrobial preservatives, antibiotics or other substances (where applicable).

CHARACTERS

The statements under the heading *Characters* are not to be interpreted in a strict sense and are not requirements.

¹² <http://www.edqm.eu/en/blood-transfusion-guides-1608.html>

This section states:

- the physical status (liquid, freeze-dried powder, frozen solid)
- the appearance of the product (e.g. colour, opalescence, viscosity)

IDENTIFICATION

This section describes how to identify the product. In plasma-derived product monographs, the Identification section generally comprises identification by immunoelectrophoresis or compliance with the limit of the assay.

TESTS

General tests for water, pH, solubility or bacterial endotoxins and other specific tests, if applicable, are prescribed and limits are given unless otherwise justified. The product must comply with these requirements throughout its shelf-life. The tests apply to the final lot and should be applicable for check analysis, for example by an Official Medicines Control Laboratory. Tests, including limits, are validated and applicable to all products available in Europe.

Purity tests (the lists of tests are provided as examples and are not exhaustive)

Typically, monographs on plasma-derived products may contain the following tests:

- pH (2.2.3);
- Osmolality (lower limit only) (2.2.35);
- Solubility;
- Water (2.5.12 or 2.5.32);
- Total protein (2.5.33);
- Protein composition;
- Molecular size distribution (2.2.30) (for polymers and aggregates).

Typically, monographs for coagulation factor preparations may contain:

- a test for activated coagulation factors, and
- a test on the heparin and/or thrombin content.

The monographs for normal immunoglobulin preparations contain additional class-specific tests:

- IgA content;
- Anti-A and anti-B haemagglutinins (2.6.20);
- Anti-D antibodies (2.6.26);
- Antibodies to hepatitis B surface antigen;

–Antibodies to hepatitis A virus.

Since other impurities/components/contamination may be clinically relevant in certain blood products, additional tests may be included:

–Prekallikrein activator;

–B19 virus DNA.

Safety tests

The monographs contain typically tests for:

–Sterility (2.6.1);

–Bacterial endotoxins (2.6.14) and/or Pyrogens (2.6.8)

Alternative test methods

The European Pharmacopoeia Commission has a policy of regular review of animal tests prescribed in monographs with a view to their replacement by *in vitro* methods wherever possible, in accordance with the *European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes*¹ with consideration of the EU Directive 2010/63/EU.

The current policy of Group 6B is to introduce, wherever possible, a provision for the use of an *in vitro* method as a preferred alternative to the pyrogen test in rabbits. Particular interests are given to the two following *in vitro* methods:

-the bacterial endotoxin test (BET) (2.6.14), and

-the monocyte-activation test (MAT) (2.6.30).

A guideline¹³ on the replacement of rabbit pyrogen testing by an alternative test for plasma-derived medicinal products was elaborated by the Biological Working Party (BWP) of the Committee for Medicinal Products for Human Use (CHMP) of the EMA. The purpose of this guidance is to highlight points to be addressed in any justification for use of a test for bacterial endotoxins as an alternative to a test for pyrogens for medicinal products derived from human blood and human plasma.

The replacement of the pyrogen test (2.6.8) by an *in vitro* method must be based on historical data and a validation is performed.

ASSAY/POTENCY

A potency test is included in each specific monograph, but it may sometimes be described in a separate chapter which is then referred to in the specific monograph.

¹³ EMEA/CHMP/BWP/452081/07

The activity of a plasma-derived product is expressed either in units of mass per volume (g/ml, or g per container) or in International Units per container or per volume.

The assay procedures may be either immunoassays for immunoglobulin preparations (described in 2.7.1 and 2.7.13) or chromogenic assays developed for coagulations factor determinations (e.g. 2.7.4). Other assays may be developed and described on a case-by-case basis.

The limit applied in the potency assay is typically 80-120 per cent of the stated potency. In some assays, where higher precision can normally be achieved, the potency is 90-110 per cent of the nominal value.

The fiducial limits of the assay are essential as an expression of the precision achieved in the specific assay. They are normally 80-125 per cent of the estimated potency when logarithmic values are used or 80-120 per cent when a linear scale is used.

The terms “estimated potency” and “stated potency” have to be understood in accordance with the definitions mentioned in the European Pharmacopoeia general chapter 5.3. *Statistical analysis of results of biological assays and tests*.

Alternative assay methods

The general statements given above on the use of alternative methods are also valid for assays that involve the use of animals.

STORAGE

This section is given for information. It gives information on storage conditions (e.g. light protection, type of glass container, vacuum or inert gas). The storage conditions are indicated by the manufacturer. They are validated by stability testing that shows the product will comply throughout the period of validity. Unless otherwise indicated in a specific monograph, the storage of products is expected to conform to that described in the relevant class-specific monograph.

LABELLING

The requirements of the labelling statements described in the relevant class-specific monograph apply to all substances or products. In some cases, additional information may be required for a particular substance or product. This information is included in the labelling section of the specific monograph and is supplementary to the requirements of the class-specific monographs.

The status of the labelling is defined in the General Notices: *“In general, labelling of medicines is subject to supranational and national regulation and to international agreements. The statements under the heading Labelling are not therefore comprehensive and, moreover, for the purposes of the Pharmacopoeia only those statements that are necessary to demonstrate compliance or non-compliance with the monograph are mandatory. Any other labelling statements are included as recommendations. When the term ‘label’ is used in the Pharmacopoeia, the labelling statements may appear on the container, the*

package, a leaflet accompanying the package, or a certificate of analysis accompanying the article, as decided by the competent authority”.

The instructions on the label are determined on a case-by-case basis. When applicable, information on how to reconstitute the product prior to use and/or information necessary for the application of a monograph is given.

4.2. MONOGRAPHS NOT COVERED BY THIS TECHNICAL GUIDE

This technical guide only covers those monographs elaborated for plasma-derived products.

Monographs covering products not derived from plasma and that might be elaborated by Group 6B, are not covered by this guide.

5. RELATIONSHIP BETWEEN CLASS-SPECIFIC MONOGRAPHS AND SPECIFIC MONOGRAPHS

The following figure illustrates the editorial relationship that exists between the drafting of monographs on plasma-derived products. This representation does not consider the functional relationship between the products.

HUMAN PLASMA-DERIVED PRODUCT MONOGRAPHS

Anticoagulants and preservative solutions for human blood (0209)

Human plasma for fractionation (0853)

Human plasma (pooled and treated for virus inactivation) (1646)

Human normal immunoglobulin for intramuscular administration (0338)

Human anti-D immunoglobulin (0557)
Human Hepatitis B immunoglobulin (0722)
Human Hepatitis A immunoglobulin (0769)
Human varicella immunoglobulin (0724)
Human rabies immunoglobulin (0723)
Human rubella immunoglobulin (0617)
Human tetanus immunoglobulin (0398)
Human measles immunoglobulin (0397)

Human normal Immunoglobulin for subcutaneous administration (2788)

Human Hepatitis B immunoglobulin (0722)

Human normal immunoglobulin for intravenous administration (0918)

Human anti-D immunoglobulin for intravenous administration (1527)
Human varicella immunoglobulin for intravenous administration (1528)
Human Hepatitis B immunoglobulin for intravenous administration (1016)

Human Coagulation factors

Human coagulation factor VII (1224)
Human coagulation factor VIII (0275)
Human coagulation factor IX (1223)
Human coagulation factor XI (1644)

Other fractionated products

Human albumin solution (0255)
Human fibrinogen (0024)
Fibrin sealant kit (0903)
Human antithrombin III concentrate (0878)
Human prothrombin complex (0554)
Human von Willebrand factor (2298)
Human α -1-proteinase inhibitor (2387)
Human C1-esterase inhibitor (2818)

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The Council of Europe is the continent's leading human rights organisation. It comprises 47 member states, 28 of which are members of the European Union. The European Directorate for the Quality of Medicines & HealthCare (EDQM) is a directorate of the Council of Europe. Its mission is to contribute to the basic human right of access to good quality medicines and healthcare and to promote and protect public health.