Technical Guide
for the elaboration and use of monographs on human plasma-derived products

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TECHNICAL GUIDE FOR THE ELABORATION AND USE OF MONOGRAPHS ON HUMAN PLASMA-DERIVED PRODUCTS

1. PURPOSE OF THE GUIDE

This document is intended to provide guidance to authors (and contributors) and users of European Pharmacopoeia (Ph. Eur.) monographs on human plasma-derived products. This applies in particular to:

- Group of Experts No. 6B (Human blood-derived products);
- authorities responsible for granting marketing authorisations for human plasma-derived products;
- Official Medicines Control Laboratories (OMCLs);
- manufacturers of human plasma-derived products;
- public and private analytical laboratories working for one of the above;
- the Secretariat of the European Pharmacopoeia and any 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. All users of the European Pharmacopoeia must be familiar with this text.

The main items relevant for human 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. 7th Edition).

As regards compliance with monographs, the General Notices state that: “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 from data derived, for example, from validation
studies of the manufacturing process and from in-process controls. Parametric release in
circumstances deemed appropriate by the competent authority is thus not precluded by the
need to comply with the Pharmacopoeia” (Ph. Eur. 7th Edition).

As regards alternative methods, 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. 7th Edition).

3.2. ALTERNATIVE METHODS

The test methods prescribed in monographs are the reference methods on which the quality
standards are based. As indicated above under Pharmacopoeial requirements, other methods
of analysis may be used for a variety of reasons. Firstly, pharmacopoeial methods have been
chosen for application to all the relevant products that were available at the time of their
elaboration. Other available methods can be used if it is demonstrated by validation that the
alternative method is equivalent to the official method or more suitable, in accordance with
the General Notices. Secondly, the methods have been developed for application in a variety
of laboratories with standard equipment but this does not rule out the use of alternative,
validated methods. Monographs are revised periodically to keep pace with progress in
techniques but pending these revisions, new methods can be used as alternatives if validated
and authorised by the competent authorities.

Use of Animals

In accordance with the provisions of the European Convention for the Protection of
Vertebrate Animals Used for Experimental and Other Scientific Purposes (1986)1 and the
European Directive2 on the same principles, Ph. Eur. 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.

3.3. GENERAL CHAPTERS AND MONOGRAPHS

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 blood
product:

1 European convention for the protection of vertebrate animals used for experimental and other scientific
provisions of the Member States regarding the protection of animals used for experimental and other scientific
Biological tests specific to plasma-derived products:

1. Prekallikrein activator (2.6.15);
2. Test for anticomplementary activity of immunoglobulin (2.6.17);
3. Anti-A and anti-B haemagglutinins (2.6.20);
4. Activated coagulation factors (2.6.22);
5. Test for anti-D antibodies in human immunoglobulin (2.6.26).

Biological assays specific to plasma-derived products:

6. Assay of human coagulation factor VIII (2.7.4);
7. Test for Fc function of immunoglobulin (2.7.9);
8. Assay of human coagulation factor VII (2.7.10);
9. Assay of human coagulation factor IX (2.7.11);
10. Assay of heparin in coagulation factors (2.7.12);
11. Assay of human anti-D immunoglobulin (2.7.13);
12. Assay of human antithrombin III (2.7.17);
13. Assay of human coagulation factor II (2.7.18);
14. Assay of human coagulation factor X (2.7.19);
15. Assay of human von Willebrand factor (2.7.21);
16. Assay of human coagulation factor XI (2.7.22);
17. Assay of human plasmin inhibitor (2.7.25);
18. Assay of human protein C (2.7.30);
19. Assay of human protein S (2.7.31);

Additional tests not restricted to blood products:

21. Sterility (2.6.1);
22. Pyrogens (2.6.8);
23. Bacterial endotoxins (2.6.14);
24. 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 the quantification of B19 Virus (B19V) DNA in plasma pools: guidelines;

– Monocyte-activation test (2.6.30).

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

3.4. HOW MONOGRAPHS AND CHAPTERS ARE ELABORATED AND UPDATED

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

Proposals to add a new text on the work programme can be made by:

– the Chair of the European Pharmacopoeia Commission;

– a delegation;

– the chair of Group 6B;

– the Secretariat of the Ph. Eur., 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.

It is the European Pharmacopoeia Commission which accepts the proposal or not, and if accepted, it adds the item 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 are usually (but not always) included in the European Pharmacopoeia only when the 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 standard even when there is only one producer.

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

Once the new monograph is drafted, the monograph is published in Pharneuropa for public enquiry. All the interested parties have 3 months to send their comments to their National Pharmacopoeial Authority (NPA), which centralises all the comments from their country. NPA然后 have 2 months to send the compiled comments to the Secretariat of the Ph. Eur. 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\(^3\).

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\(^3\) [www.edqm.eu/ht](http://www.edqm.eu/ht)

\(^4\) [Rules of procedure of the European Pharmacopoeia Commission_PA/PH/SG (07) 4 COM 1R. Council of Europe, European Directorate for the Quality of Medicines & HealthCare (2007).](http://drt.edqm.eu)

\(^5\) [http://drt.edqm.eu](http://drt.edqm.eu)
The Secretariat makes a consolidated document from all these comments.

The consolidated comments are then examined by Group 6B at the meeting following the end of the consultation period.

After the study of these comments, if there is no major change in the text and if no restrictions are added to the text published for comment, the text is proposed for adoption at the next Commission session. If there is a major change in the text or if restrictions are added, the text is published again for public enquiry in *Pharmeuropa*.

If the text is adopted, it is published in the European Pharmacopoeia 6 months after the Commission session, and implemented 6 months later. Should the text not be adopted, either it will go back to the group or no specific monograph on this particular product will be published in the European Pharmacopoeia.

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

Proposals to revise a text can be made by:

- the Chair of the European Pharmacopoeia Commission;
- a delegation;
- the chair of Group 6B;
- the Secretariat of the Ph. Eur., for example on the basis of information and data provided via the Helpdesk³ by a manufacturer or by a user of the European Pharmacopoeia.

It is the European Pharmacopoeia Commission that refers requests for revision to the relevant Group of Experts (see the *Rules of Procedure of the European Pharmacopoeia Commission*⁴).

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

During the revision of a monograph, the standards attained by blood products that are already on the market will be taken into consideration.

Once the monograph is revised, it is published in *Pharmeuropa* for public enquiry. The interested parties have 3 months to send their comments to their NPA, which centralises all the comments of their country. NPAs then have 2 months to send the compiled comments to the Secretariat of the Ph. Eur. via the DRT⁵. Manufacturers outside Europe and pan-European organisations have 3 months to send their comments to the Secretariat of the Ph. Eur. via the Helpdesk³. The Secretariat makes consolidated comments from all these comments.

The consolidated comments are studied by Group 6B at the meeting following the end of the consultation period.

After the study of these comments, if there is no major change in the text and if no restrictions are added to the text published for comments, the text is proposed for adoption at the next Commission session. If there is a major change in the text or if restrictions are added, the text is published again for public enquiry in *Pharmeuropa*.
If the revised text is adopted, it is published in the European Pharmacopoeia 6 months after
the Commission session, and implemented 6 months later. Should the text not be adopted, it
will either go back to the group for further study/revision or stay as it is and not be revised.

4. CONTENT OF THE MONOGRAPHS

4.1. STRUCTURE AND CONTENT OF THE MONOGRAPHS ON HUMAN 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 monographs, where one exists.

The provisions of the “base” monographs, i.e. Human plasma for fractionation (0853),
Human normal immunoglobulin (0338) and Human normal immunoglobulin for intravenous
administration (0918) apply to all fractionated products, human normal specific
immunoglobulin and human normal specific immunoglobulin for intravenous administration,
respectively, including those for which there is no specific monograph. The base monographs
prescribe essential requirements which supplement and expand on requirements contained in
the monographs on specific products. The authors and users of specific monographs must be
familiar with the contents of the relevant monographs in order to be able to draft or use the
specific monographs correctly.

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

The specific monographs must be used and applied, taking account of the explanations,
guidance and requirements given in all documents mentioned above, including the base
monographs.

It is expected that the test 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

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

4.1.2. Sections of the monographs

The various sections are mandatory, with the exception of the Storage section and for some
items, the Labelling section.

Informational statements are identified by their content and drafting style. See also the
General Notices (current edition of the Ph. Eur.).

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6 www.ema.europa.eu/htms/human/humanguidelines/biologicals.htm and
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);
- whether excipients, stabilisers and other auxiliary substances are allowed, and examples of these substances might be provided;
- the potency or specific biological activity, whichever applicable;
- for specific immunoglobulins: exceptions and/or additions to the requirements for normal immunoglobulin preparations.

Substances allowed are included in the Definition section. By default, should a substance or class of auxiliary substances (excipients, stabilisers, other ingredients, etc) not be mentioned in the Definition section, it should be considered as 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 that 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. Only the “base” monographs apply in this case.

PRODUCTION

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

This section is primarily addressed to manufacturers to provide advice. Apart from the monograph on Human plasma for fractionation (0853), monographs on blood-derived
products in the Ph. Eur. cover 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 Ph. Eur. Nevertheless, the principles described in the Guide to the preparation, use and quality assurance of blood components (current edition) 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 (list not exhaustive, 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 (whenever applicable).

CHARACTERS

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

This section states:

- the physical status (liquid, dry 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 an immunoelectrophoresis or should comply with the limit of the assay.

TESTS

General tests, e.g. water, pH, solubility, pyrogens or bacterial endotoxins and other specific tests if applicable, are described and limits are given unless otherwise justified. The product should 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 control laboratory. Tests, including limits, should be validated and should be 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 polymer 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);
- Pyrogens (2.6.8) and/or Bacterial endotoxins (2.6.14).

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 and with the EU Directive 86/609/EEC².

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 pyrogens test in rabbits. Particular interests are given to the following 2 *in vitro* methods:

- the bacterial endotoxins test (BET) (2.6.14), and
- the monocyte-activation test (2.6.30).

A guideline⁷ on the replacement of rabbit pyrogen testing by an alternative test for plasma-derived medicinal products was elaborated by the Biologics 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 the 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 should be performed.

**ASSAY/POTENCY**

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

The activity of a plasma-derived product is to be expressed either in units of mass per volume (e.g., 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. In some assays, where higher precision normally can be achieved, the potency should be 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 shall normally be 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 Ph. Eur. 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 use of animals.

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² EMEA/CHMP/BWP/452081/2007
STORAGE

This section is given for information. It gives information on storage conditions (e.g. protection from light, type of glass container, vacuum or inert gas). The storage conditions are indicated by the manufacturer. They have been validated by stability testing that showed that 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 base monograph.

LABELLING

The appropriate requirements of the labelling statements described in the base monograph apply to all products. In some cases additional information may be necessary for a particular product. This information is then included in the Labelling section of the specific monograph and this is supplementary to the requirements of the base 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 shall be given of how to reconstitute the product prior to use, or contain information necessary for the application of monograph.
4.2. **MONOGRAPHS NOT COVERED BY THIS TECHNICAL GUIDE**

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

Monographs covering products not derived from plasma and that might be elaborated by Group 6B, are not covered by the present Technical Guide.

5. **RELATIONSHIP BETWEEN BASE 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 for fractionation (0853)

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

**Human normal immunoglobulin (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 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)