CONTROL AUTHORITY BATCH RELEASE OF BLOOD PRODUCTS

2001

Clotting Factor Concentrates, Plasma Inhibitor Concentrates and Fibrin Sealants

Guideline title	**Official Control Authority Batch Release of Clotting Factor Concentrates, Plasma Inhibitor Concentrates and Fibrin Sealants**
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Custodian Organisation	**The present document was elaborated by the EDQM in the OMCL network and finalised under PA/PH/OMCL (2001) 14, DEF**

OFFICIAL CONTROL AUTHORITY BATCH RELEASE OF CLOTTING FACTOR CONCENTRATES, PLASMA INHIBITOR CONCENTRATES AND FIBRIN SEALANTS

1 Introduction

Control Authority Batch Release of medicinal products derived from human blood and plasma is performed within the framework of Article 4.3 of Directive 89/381/EEC and following the current Guideline on EC Administrative Procedure for Official Control Authority Batch Release.

Requirements are given in the general monograph 'Human plasma for fractionation (0853)' of the European Pharmacopoeia (Ph. Eur.) and in the relevant monographs:

Ph. Eur. monograph title	**Ph. Eur. monograph N°**
Human Coagulation Factor IX, freeze-dried	1223
Human Coagulation Factor VIII, freeze-dried	0275
Human Coagulation Factor VII, freeze-dried	1224
Human Prothrombin Complex, freeze-dried	0554
Fibrin Sealant Kit	0903
Human Fibrinogen, freeze-dried	0024
Human Antithrombin III Concentrate, freeze-dried	0878

2 Sampling and tests to be performed by the Control Laboratory

The following samples should be supplied to the Official Medicines Control Laboratory performing batch release:

At least 5 samples of 1.5 ml each of each manufacturing plasma pool involved in the production of this batch

If the plasma pools have already been tested by a Control Authority, the submission of a copy of the certificate of approval is sufficient.

Plasma pool samples should stored at –20 °C and shipped on dry ice.

and

An appropriate number of finished product, not less than 4.

The Control Laboratory should perform the following tests:

On the manufacturing plasma pools:

For virological markers : anti-HIV 1 and 2, HBsAg, anti-HCV and HCV RNA as determined by NAT.

On the finished product :

Factor VII :

- solubility and appearance
- potency
- F VIIa (where necessary)

Factor VIII :

- solubility and appearance
- potency
- vWF : Ag test*
- vWF function*

* should be performed for all products with an indication for vWD. The specific method used (e.g. antigen, vWF: ristocetin cofactor or collagen binding) depends on which is declared by manufacturer.

Single Factor IX:

- solubility and appearance
- potency
- Activated Coagulation Factors (NAPTT)

Factor XIII:

- solubility and appearance
- potency

Prothrombin Complex (PCC):

- solubility and appearance
- potency (FIX)
- Activated Coagulation Factors (F IIa, NAPTT)

Activated Prothrombin Complex (aPCC) :

- solubility and appearance
- potency

Antithrombin III :

- solubility and appearance
- potency

α_1-Proteinase-Inhibitor:

- solubility and appearance
- potency

C1-Inhibitor :

- solubility and appearance
- potency

Fibrinogen :
- solubility and appearance
- potency
- Stability after reconstruction

Fibrin Sealant Kit :

Fibrinogen :
- solubility and appearance
- potency (F XIII, Fibrinogen)
- Stability after reconstitution

Thrombin :
- solubility and appearance
- potency

3 Protocol submission

A model protocol is given below. A protocol for specific product may differ in detail but it is essential that all relevant details demonstrating compliance with the Marketing Authorisation and the Ph Eur monograph should be given. WHO requirements may also serve as the model for the content and presentation of the protocol data. Results of the tests are required (pass or fail is not sufficient, results of retest if applicable should be given). Sufficient detail should be supplied to allow recalculation of test values. Specifications for each test and dates when they were performed should also be included. Results of qualification tests on reference materials should be given for each new in-house reference material.

3.1 Summary information on the batch of finished product

Trade name: ……..

Non-proprietary name (INN)/Ph Eur name/ common name of product (whichever is appropriate): ……..

Batch number(s): ……..

Finished product (final lot): ……..

Final bulk: ……..

Type of container: ……..

Total number of containers in this batch: ……..

Date of expiry: ……..

Storage temperature: ……..

Marketing Authorisation number issued by (Member State/EU):
……..

Name and address of manufacturer: ……..

Name and address of Marketing Authorisation Holder if different:
……..

3.2 Production information

Site of manufacture: ……..

Date of manufacture: ……..

Summary information scheme on batch specific production data including dates of different production stages, identification numbers and blending scheme (see 3.2.3.).

Viral inactivation

Batch No . . . . has been subjected to a viral inactivation treatment by the following process: (give details such as solvent, detergent, concentrations, temperature, time, dry heat, pasteurisation, etc. as appropriate), according to the method described in the Marketing Authorisation (M.A.).

3.2.1 Starting materials

Individual donations

Source country of donations
remuneration : yes/no
Individual donations were each tested negative for :

viral marker	**method**	**test kit generation**	**brandname**
anti-HIV 1/2			
Hepatitis BsAg			
anti-HCV			

The same information should also be given when applicable for:
Alanine Amino-Transferase
Anti-Treponema

The test methods are those approved in the licence application.

3.2.2 Plasma pools

Code number(s) of plasma pool(s):……
Date of manufacture:……..
Volume of pool / number of donations:…….
Source country and supplier of plasma pool:…….
This plasma pool has been obtained from the combination of individual donations originated from the following donation / plasmapheresis centres (give the list of the addresses of these centres and the period of collection for each pool):…….
Tests for viral markers : this batch was manufactured from plasma pools which each tested negative for:

viral marker	**method**	**test kit generation**	**brand name**	**date of testing**
anti-HIV 1/2				
Hepatitis BsAg				
anti-HCV				
HCV RNA by NAT				

Other tests as laid down in the Marketing Authorisation, e.g. protein, bacterial count, . . .
OMCL testing on manufacturing plasma pool was performed by: . . . .
A copy of the certificate of approval should be submitted.

3.2.3 Intermediate product

(if applicable, e.g. cryoprecipitate, fraction II)

Manufacturer: ……
Identification number: ……
Amount:
Date of manufacture: ……
Storage temperature, storage time and approved storage period (as laid down in the Marketing Authorisation, see summary of information scheme 3.2): ……
Tests on intermediate (if applicable): ……
Lot numbers of plasma pool used in the production (details of this lot should be specified as under 3.2.1 and 3.2.2.):……

3.2.4 Blending of final bulk

3.2.4.1 Composition of final bulk

Date of blending, identification code of ingredients : bulk active ingredients, stabilisers, preservatives, other components.
Final bulk container : identification code and quantity.

3.2.4.2 Control tests on final bulk

As specified in the Marketing Authorisation

3.2.4.3 Excipients derived from human blood

The information on excipients should not be less detailed than the information requested for an active ingredient regarding documentation of starting materials as well as specifications and tests on the final product. Nevertheless, if the batch of excipient has been released by an OMCL in accordance with the Official Authority Batch Release procedure, the submission of a copy of the batch release certificate is sufficient.

3.3 Finished product

3.3.1 Identification of the batch of finished product

Date and reference of manufacture: ……..

Date of filling: ……..

Type of container: ……..

Number of containers after inspection: ……..

Filling volume: ……..

Date of start of period of validity: ……..

Expiry date: ……..

3.3.2 Composition of the finished product

Composition of 1 ml of solution (1 ml solution contains . . .)

3.3.3 Control tests on finished product

Depending on the Marketing Authorisation and the Ph. Eur. monographs, a certificate of analysis should include the following:

- Identity
  e.g. species specific antisera tests, assay (potency)
- Purity
  e.g. sterility, pyrogens, endotoxin content, solubility, total protein, pH, Aluminium, protein composition, antigen content, residual moisture, osmolality, appearance, specific activity, heparin, stabilisers, electrolytes, heparin binding fraction (antithrombin III), residual solvent/detergent, haemagglutinin, activated coagulation factors (NAPTT, thrombin), protein nitrogen content, viral markers.
- Potency
  Testing address and brief description of test method and principle should be indicated. Reference to test instruction and validation study in the dossier should be given.

Reference material

- Type of Standard
- Batch number
- Storage conditions

If other than official standard (e.g. in-house reference material) please indicate the following information :

- Calibrated against
- Original calibration date
- Calibration value assigned
- Recalibration date and result

Product

- Product test date
- N° of bottles tested
- Results of individual assays (potency and 95% fiducial limit)
- Combined potency estimates (potency and 95% fiducial limit)
- Method of combination
- Potency assigned to batch

4 Certification

Certification by qualified person taking the overall responsibility for production and control:

I herewith certify that _____(name of the product) batch N°_____ was manufactured and tested according to the procedures approved by the competent authorities and complies with the quality requirements. This includes that, for any materials derived from ruminants (bovine, ovine, caprine) used in the manufacture and/or formulation of the batch of product specified above, all measures have been taken to demonstrate compliance with Directive 1999/82/EEC.

Name: _____

Function: _____

Date: _____

Signature:_____