EUROPEAN COMMISSION
DIRECTORATE-GENERAL III
INDUSTRY
Industrial affairs III: Consumer goods industries
Pharmaceutical products and Cosmetics
Head of Unit

Brussels, 29 May 1998
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To Consultation Partners

Subject: **Manufacture of medicinal products derived from human blood or plasma**

Dear Colleague,

The attached document is a draft revision of the 1992 text of Annex 14 to the EU Guide to Good Manufacturing Practice - Eudralex Volume IV.

It has been drafted in consultation with Member States Inspectors within the Expert Group on Inspections and Control of Medicinal Products.

I would appreciate receiving your comments by 31 August 1998.

Yours sincerely,

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Working Party on Control of Medicines and Inspections

Title: Manufacture of medicinal products[1] derived from human blood or plasma

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Pharmaceutical Committee (for information)	16 March 1998
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[1] Council Directive 89/381/EEC of 14 June 1989 extending the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products and laying down special provisions for medicinal products derived from human blood or human plasma (OJ No L 181 of 28.6.1989)

Manufacture of medicinal products derived from human blood or human plasma

Principle

Medicinal products derived from human blood or plasma have certain special features arising from the biological nature of the source material. For example, disease-transmitting agents, especially viruses, may contaminate the source material. The safety of these products relies therefore on the control of source materials and their origin as well as on the subsequent manufacturing procedures, including virus removal and inactivation.

The general chapters of the guide to GMP apply to medicinal products derived from human blood or plasma, unless otherwise stated. Some of the Annexes may also apply, e.g. manufacture of sterile medicinal products, use of ionising radiation in the manufacture of medicinal products and manufacture of biological medicinal products.

Since the quality of the final products is affected by all the steps in their manufacture, including the collection of blood or plasma, all operations should therefore be done in accordance with an appropriate system of Quality Assurance and current Good Manufacturing Practice.

By virtue of Directive 89/381/EEC, the necessary measures shall be taken to prevent the transmission of infectious diseases by application of the monographs of the European Pharmacopoeia regarding blood and plasma. These measures shall also comprise those currently recommended by the Council of Europe (see "Guide to the preparation, use and quality assurance of blood components", Council of Europe Press) and by the World Health Organisation (see report by the WHO Expert Committee on Biological Standardisation, WHO Technical Report Series 840, 1994).

This annex should also be read in conjunction with the guidelines adopted by the CPMP, in particular "Medicinal products derived from human blood and plasma", "Validation of virus removal and inactivation procedures" (Vol. III, addendum 2 of the series "The rules governing medicinal products in the European Community") and "Contribution to the part of the marketing authorisation application dossier: control of starting materials for the manufacture of medicinal products derived from blood" (Vol. II of the series "The rules governing medicinal products in the European Community").

Many of the provisions of this annex apply equally to blood components and plasma derivatives. It should however be noted that blood components are presently not covered by EC directives.

Glossary

Blood products:	any medicinal product derived from human whole blood or plasma donations.
Blood components:	Therapeutic components of blood (red cells, white cells, plasma, platelets), that can be prepared by centrifugation, filtration and freezing using conventional blood bank methodology
Plasma derivatives:	highly purified human plasma protein prepared under licensed pharmaceutical manufacturing conditions
Sterile Connecting Device:	connects two tubes without breaching the sterility of the inside of the tubes.

Quality Management

1. Quality Assurance should cover all stages leading to the finished product, from collection (including donor selection, blood bags, anticoagulant solutions and test kits) to storage, transport, processing, quality control and delivery of the finished product, all in accordance with the texts referred to under Principle at the beginning of this Annex.
2. Blood or plasma used as a source material for the manufacture of medicinal products should be collected in centres subject to inspection and approved by a competent authority.
3. Procedures to determine the suitability of individuals to donate the blood and plasma, used as a source material for the manufacture of medicinal products, and the results of the testing of their donations should be documented by the collection establishment and should be available to the manufacturer of the medicinal product.
4. Monitoring of the quality of medicinal products, derived from human blood or plasma, should be carried out in such a way that any deviations from the quality specifications can be detected.
5. Medicinal products, derived from human blood or plasma, which have been returned unused should normally not be re-issued (see also point 5.65 of the main GMP guide).

Premises and Equipment

6. The premises used for the collection of blood or plasma should be of suitable size, construction and location to facilitate their proper operation, cleaning and maintenance. Collection and processing of blood and plasma should not be performed in the same area. There should be suitable donor interview facilities so that these interviews are carried out in private.
7. The preparation of blood components which involves the breach of the closed system should be performed in a grade D environment with a grade B background (see Annex 1) unless a Sterile Connecting Device is used.
8. Manufacturing and testing equipment should be designed, validated and maintained to suit its intended purpose and should not present any hazard to donors, products or operators. Regular maintenance and calibration should be carried out according to established procedures.

9. In the preparation of plasma fractions, viral inactivation or removal procedures are used and steps should be taken to prevent cross contamination of treated with untreated products; dedicated and distinct premises and equipment should be used for treated products.

Blood and Plasma collection

10. The method used to disinfect the skin of the donor should be clearly defined and shown to be effective. Adherence to that method should then be maintained.
11. Each donor must be positively identified at reception and again before venepuncture. A third identification, preferably by a signature check, will be necessary during manual apheresis, where components are being returned after disconnection.
12. Donation number labels must be re-checked independently to ensure that those on blood packs, sample tubes and donation records are identical.
13. Blood bag and apheresis systems should be inspected before use for damage or contamination.
14. While fully respecting confidentiality, there must be a system in place which enables the path taken by each donation to be traced, both forward from the donor and back from the finished medicinal product, including the customer (hospital or health care professional). It is normally the responsibility of this customer to identify the recipient.
15. Post-collection measures: A standard operating procedure describing the mutual information system between the blood collection centre and the manufacturing or fractionation centre should be set up so that they can inform each other if:
    - it is found subsequent to donation that the donor did not meet the current donor health criteria;
    - it is determined that subsequent to donation, a donor may be at risk of transmitting an infectious disease;
    - it is discovered that testing for viral markers has not been carried out according to agreed procedures;
    - the donor seroconverts or develops an infectious disease as a result of a transmissible agent (HBV, HCV and other non-A, non-B, non-C hepatitis viruses, HIV 1 and 2 and other agents in the light of current knowledge);
    - the recipient develops post-transfusion/infusion infection which implicates or can be traced back to the donor.

In these cases, a re-assessment of the batch documentation should always be carried out. The need for withdrawal of the given batch should be carefully considered, taking into account criteria such as the transmissible agent involved, the size of the pool, the time period between donation and seroconversion, the nature of the product and its manufacturing method.

Production and Quality Control

16. The specified storage temperatures of blood, plasma and intermediate products during transportation from collection centres to manufacturers or between different manufacturing sites should be checked and validated. The same applies to delivery of these products.

17. Before any blood and plasma donations, or any product derived therefrom, are released for issue and/or fractionation, they should be tested using an appropriate and validated test method and found non reactive for the following markers of specific disease-transmitting agents:
    - HBsAg;
    - antibodies to HIV 1 and HIV 2;
    - antibodies to HCV.

    (Additional tests may form part of national requirements)

18. The first homogeneous plasma pool (e.g. after separation of the cryoprecipitate) should be tested using an appropriate and validated test method and found non reactive for the following markers of specific disease-transmitting agents:
    - HBsAg;
    - antibodies to HIV 1 and HIV 2;
    - antibodies to HCV.

19. Testing requirements for other viruses should be considered in the light of knowledge emerging as to infectious agents and the availability of appropriate test methods.

20. The labels on single units of plasma stored for pooling and fractionation must comply with the provisions of the European Pharmacopoeia monograph "Human plasma for fractionation" and bear at least the identification number of the donation, the name and address of the plasma collection centre or the references of the blood transfusion service responsible for preparation, the batch number of the container, the storage temperature, the total volume or weight of plasma, the type of anticoagulant used and the date of collection and/or separation.

21. In order to minimise the microbiological contamination of plasma for fractionation or the introduction of foreign material, the pooling and thawing should be performed at least in a grade D clean area, wearing the appropriate clothing and in addition face masks and gloves should be worn. Methods used for opening bags, pooling and thawing should be regularly monitored, e.g. by testing for bioburden.

22. Products which have undergone a process of virus removal or inactivation should be clearly differentiated from those which have not.

23. Validation of methods used for virus removal or virus inactivation should not be conducted in the production facilities in order not to put the routine manufacture at any risk of contamination with the viruses used for validation.

Retention of samples

24. Samples of each pool of plasma should be stored under suitable conditions for at least one year after the expiry date of the finished product with the longest shelf-life.