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Working Party on Control of Medicines and Inspections

Revision of **Annex 14** to the EU Guide to Good Manufacturing Practice

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

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

Principle

In accordance with Directive 75/318/EEC[2], for biological medicinal products derived from human blood or plasma, starting materials include the source materials such as cells or fluids including blood or plasma. 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, manufacture of biological medicinal products and computerised systems.

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 and the requirements and standards of the European Pharmacopoeia monographs regarding plasma for fractionation and medicinal products derived from human blood or plasma shall be applicable. These measures shall also comprise the Council Recommendation of 29 June 1998 "On the suitability of blood and plasma donors and the screening of donated blood in the European Community[3] (98/463/EC), the recommendations of the Council of Europe (see "Guide to the preparation, use and quality assurance of blood components", Council of Europe Press) and 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 "Note for guidance on plasma-derived medicinal products (CPMP/BWP/269/95

[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)

[2] Council Directive 75/318/EEC, of 20 May 1975, on the approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products (OJ No L 147 of 9.6.1975, p. 1) as last amended by Council Directive 93/39/EEC (OJ No L 214 of 24.8.1993, p. 22).

[3] O.J. L 20321.7.1998 p. 14

rev.2)", "Virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses" published in Volume 3A of the series "The rules governing medicinal products in the European Community") and "Contribution to part II of the structure of the dossier for applications for marketing authorisation - control of starting materials for the production of blood derivatives"(III/5272/94).

These documents are regularly revised and reference should be made to the latest revisions for current guidance.

The provisions of this annex apply to medicinal products derived from human blood and plasma. They do not cover blood components used in transfusion medicine, since these are presently not covered by EC directives. However many of these provisions may be applicable to such components and competent authorities may require compliance with them.

Glossary

Blood:	Whole blood collected from a single donor and processed either for transfusion or further manufacturing
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
Medicinal product derived from blood or plasma:	Same meaning as that given in Directive 89/381/EEC

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 by establishments and be tested in laboratories which are subject to inspection and approved by a competent authority.

3. Procedures to determine the suitability of individuals to donate 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, processing and testing 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. Manufacturing, collection and testing equipment should be designed, qualified and maintained to suit its intended purpose and should not present any hazard. Regular maintenance and calibration should be carried out and documented according to established procedures.

8. In the preparation of plasma-derived medicinal products, 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

9. A standard contract is required between the manufacturer of the medicinal product derived from human blood or plasma and the blood/plasma collection establishment or organisation responsible for collection. Guidance on the content of the standard contract is provided in "Contribution to part II of the structure of the dossier for applications for marketing authorisation - control of starting materials for the production of blood derivatives"(III/5272/94)

10. Each donor must be positively identified at reception and again before venepuncture; see also Council Recommendation of 29 June 1998 on the suitability of blood and plasma donors and the screening of donated blood in the European Community[4] (98/463/EC).

11. 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.

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 for damage or contamination before being used to collect blood or plasma. In order to ensure traceability, the batch number of blood bags and apheresis systems should be recorded.

Traceability and post collection measures

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.

[4] O.J. L 20321.7.1998 p. 14

15. Post-collection measures: A standard operating procedure describing the mutual information system between the blood/plasma collection establishment and the manufacturing/fractionation facility should be set up so that they can inform each other if, following donation:

    - it is found that the donor did not meet the relevant donor health criteria;
    - a subsequent donation from a donor previously found negative for viral markers is found positive for any of the viral markers;
    - it is discovered that testing for viral markers has not been carried out according to agreed procedures;
    - the donor has developed an infectious disease caused by an agent potentially transmissible by plasma-derived products (HBV, HCV, HAV and other non-A, non-B, non-C hepatitis viruses, HIV 1 and 2 and other agents in the light of current knowledge);
    - the donor develops Creutzfeldt-Jakob disease (CJD or vCJD);
    - the recipient of blood or a blood component develops post-transfusion/infusion infection which implicates or can be traced back to the donor.

    The procedures to be followed in the event of any of the above should be documented in the standard operating procedure. Look-back should consist of tracing back of previous donations for at least six months prior to the last negative donation. In the event of any of the above, 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. Where there are indications that a donation contributing to a plasma pool was infected with HIV or hepatitis A,B or C, the case should be referred to the relevant competent authority(ies) responsible for the authorisation of the medicinal product and the company's view regarding continued manufacture from the implicated pool or of the possibility of withdrawal of the product(s) should be given. More specific guidance is given in the current version of the CPMP Note for Guidance on plasma-derived medicinal products.

Production and Quality Control

16. Before any blood and plasma donations, or any product derived therefrom, are released for issue and/or fractionation, they should be tested, using a validated test method of suitable sensitivity and specificity, for the following markers of specific disease-transmitting agents:

    - HBsAg;
    - antibodies to HIV 1 and HIV 2;
    - antibodies to HCV.

    If a repeat-reactive result is found in any of these tests, the donation is not acceptable.

    (Additional tests may form part of national requirements)

17. The specified storage temperatures of blood, plasma and intermediate products when stored and during transportation from collection establishments to manufacturers, or

between different manufacturing sites, should be checked and validated. The same applies to delivery of these products.

18. The first homogeneous plasma pool (e.g. after separation of the cryoprecipitate) should be tested using a validated test method, of suitable sensitivity and specificity, and found non reactive for the following markers of specific disease-transmitting agents:

    - HBsAg;
    - antibodies to HIV 1 and HIV 2;
    - antibodies to HCV.

    Confirmed positive pools must be rejected.

19. Only batches derived from plasma pools tested and found non-reactive for HCV RNA by nucleic acid amplification technology (NAT), using a validated test method of suitable sensitivity and specificity, should be released.

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

21. 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 collection establishment 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.

22. In order to minimise the microbiological contamination of plasma for fractionation or the introduction of foreign material, the thawing and pooling 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. The cleanroom requirements for all other open manipulations should conform to the requirements of Annex 1 of the EU guide to GMP.

23. Methods for clearly distinguishing between products or intermediates which have undergone a process of virus removal or inactivation, from those which have not, should be in place.

24. 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

25. Where possible, samples of individual donations should be stored to facilitate any necessary look-back procedure. This would normally be the responsibility of the collection establishment. 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.

Disposal of rejected blood, plasma or intermediates

26. There should be a standard operating procedure for the safe and effective disposal of blood, plasma or intermediates.