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**EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION**  
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**Proposal to Update the WHO Requirements for the collection, processing  
and quality control of blood, blood components and plasma derivatives**

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WHO's technical position regarding quality and safety of blood products is set out in the WHO Requirements for the collection, processing and quality control of blood, blood components and plasma derivatives. These Requirements have continuously been updated since 1976, the last revision being in 1992, and published in the Technical Report Series No. 840, 1994, Annex 2. The requirements define a quality assurance system based on the existence of a national structure independent from manufacturers as well as the principles of quality assurance for biological products i.e. control of starting material, production process and final product supported by strict adherence to Good Manufacturing Practices. The WHO Requirements, which are used by medicines regulatory authorities and manufacturers, are included in national regulations as well as in regional legal binding documents such as the European Pharmacopoeia and the European Blood Directive.

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The structure of the current document, which covers the various requirements associated to the collection, selection and processing of blood and plasma products, can be summarized as follows:

Part A: requirements for collection of source material (premises, equipment, personnel, donors and collection of blood or plasma)

Part B: requirements for single donor and small pool products (production and control)

Part C: requirements for large pool products (production facilities, equipment, provision of support services, personnel, production control and control of albumin and plasma protein fraction, immunoglobulins and coagulation-factor concentrates)

Part D: national control requirements, release and certification

During the last five years, the Expert Committee on Biological Standardization (ECBS) and relevant national regulatory authorities have been consulted about the need to update the above mentioned WHO Requirements to take on board the major scientific and technical developments in the blood products field since the document was last revised in 1992. The document has also been discussed at the last two International Conferences of Drug Regulatory Authorities, organized by WHO in 1999 and 2002. In both Conferences, WHO was requested to extend efforts to upgrade the quality and safety of blood products and to support and strengthen their national regulatory authorities and control laboratories in order to increase their competence in this area.

Based on the feed-back obtained from the consultations indicated above, a conservative approach was taken in 1999 to produce complementary guidance documents which would fill the main gaps of the current WHO Requirements. An example of such a guidance document is the WHO Guideline on Viral Inactivation and Removal Procedures, adopted at the 52 ECBS Meeting in November 2001. These Guidelines pertain to the validation and assessment of viral inactivation and removal steps employed during the manufacturing of human blood plasma derivatives and virally inactivated plasma for transfusion, either prepared from plasma pools or from individual donations. This WHO Guideline will support the Quality Assurance capacity building activities for Medicines Regulatory Authorities and is expected to have significant impact on the implementation of quality assurance systems in the introduction of viral inactivation procedures and the validation of these processes.

It should be recognized that the current requirements cover a wide range of subjects and methodologies and some of the wording used could lead today to misinterpretation, especially in areas where the degree of information and understanding of the field may be insufficient. Also, a number of gaps have been identified notably related to quality aspects of plasma as a source material of medicinal products. These include the selection criteria for blood/plasma donors, donation and (plasma) pool testing/screening policies, the epidemiology of transmissible diseases among blood donors, processing of plasma, inventory management, GMP for blood/plasma collection centres, requirements for inspection by local control authorities and issues related to the licensing and approval of blood and plasma collection centres.

Continuing concerns about the quality and safety of blood products have resulted in a number of urgent requests from Member States for support and advice from WHO. The development of a WHO Guideline or guidance document addressing the issues listed above would provide a reliable body of information, based on recognized experience and technology, which would help both medicines regulatory authorities and manufacturers to select and decide about the most appropriate processes and technologies. Furthermore, such a guideline would serve to speed implementation of production and control processes and ensure that the implementation is appropriate.

### **PROPOSALS FOR THE UPDATING PROCESS**

Up till the latest revision of the “WHO Requirements for the collection, processing and quality control of blood, blood components and plasma derivatives” in 1992 the policy has been to update the document as a whole. In the last five years, priorities for the development of complementary guidance to the above Requirements were identified in two main areas:

- Viral inactivation and removal procedures intended to assure the viral safety of human blood plasma products (adopted by the ECBS in 2001)
- Collection, processing and quality control of human plasma, including the preparation of a Plasma Master File (proposed)

It is now proposed to the Committee to prepare a complementary document to the WHO requirements as WHO guidelines specifically dealing with the collection, processing and quality control of Human Plasma. This document should also address the preparation of a Plasma Master File, which during the last years has become part of the regulatory process in several countries.

Alternatively, a complete review and replacement of the current WHO requirements (except for Viral inactivation/removal procedures) could be considered. However, the feasibility of this approach might prove to be difficult and may lack sufficient justification.

### **REQUEST TO THE COMMITTEE:**

The Committee is therefore requested to discuss the strategy for the updating of the current WHO Requirements. In both cases, either complete replacement of the current WHO Requirements or development of complementary WHO Guidelines on the Quality and Safety of Plasma and issues related to the Plasma Master File, an appropriate schedule for the development of these Guidelines should also be considered.

**REFERENCES**

The WHO Guidelines and other documents related to the WHO Requirements for the collection, processing and quality control of blood, blood components and plasma derivatives are listed below:

Guidelines on Good Manufacturing Practices for biological products. In: WHO Expert Committee on Biological Standardization . 42<sup>nd</sup> Report.  
WHO Technical Report Series No 822, 1992, Annex 1.

Guidelines for national authorities on quality assurance for biological products  
In: WHO Expert Committee on Biological Standardization . 42<sup>nd</sup> Report.  
WHO Technical Report Series No 822, 1992, Annex 2.

Good manufacturing practices for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. 32<sup>nd</sup> Report.

WHO Technical Report Series No 822, 1992, Annex 1.

Guidelines on Regulation and licensing of biological products in countries with newly developing Regulatory Authorities. In: WHO Expert Committee on Biological Standardization. 45<sup>th</sup> Report. WHO Technical Report Series TRS No 858, 1994, Annex 1.

IX International Conference of Drug Regulatory Authorities (ICDRA).  
Workshop on Safety Issues of plasma-derived medicinal products, Berlin, 28 April 1999:  
Recommendations published in WHO Drug Information, Vol. 13 No. 2, 1999.

Guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood plasma products. In: WHO Expert Committee on Biological Standardization. 52<sup>nd</sup> Report, 2001. WHO Technical Report Series (In press).

X International Conference of Drug Regulatory Authorities (ICDRA).  
Workshop on Safety of blood derived products, Hong-Kong, 24-27 June 2002.  
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