

# Information Sheet

## *Ensuring the Quality and Safety of Plasma Derived Medicinal Products*

### Scope

**This information sheet is intended to provide advise to National Medicine Regulatory Authorities, blood transfusion services, policy makers in national health authorities, manufacturers of plasma derived medicinal products and interested parties on the fundamental aspects supporting the quality and safety of these products.**

### Plasma Derived Medicinal Products

Plasma derived medicinal products are manufactured from human blood plasma (*plasma*). Plasma can be obtained from whole blood donations (*recovered plasma*) or by apheresis procedures (*source plasma*). Plasma is the source of a wide range of medicinal therapeutic products that are used for the treatment and prevention of a variety of life-threatening injuries and diseases often associated with protein deficiency states.

Improvements in protein purification technology (*fractionation*) over recent years have made available a wide variety of human plasma proteins that include:

- Coagulation factors
- Immunoglobulins
- Albumin
- Fibrin sealants

The transmission of blood-borne pathogens, such as hepatitis and Human Immunodeficiency Virus (HIV) are of particular concern in the manufacture of plasma derived medicinal products. A batch of starting plasma containing a single contaminated unit of plasma potentially can transmit a blood-borne disease to a large number of recipients.

From the contaminated plasma pool multiple intermediate products and subsequently numerous batches of final product can be manufactured. Therefore, the safety of products manufactured from plasma, is dependent on the measures taken to minimise the contamination of the starting material (donor selection, screening and testing). Safety is enhanced by the application of virus inactivation procedures and technology that removes or reduces the level of blood-borne viruses and other infectious agents.

The national Medicines Regulatory Authorities (MRAs) are responsible for the regulation of plasma derived medicinal products. Over the past decades, they have been faced with serious and complex challenges at a scientific, technological and regulatory level to ensure that these biological products are of good quality, safety and efficacy.

### Quality Assurance Principles

Conventional pharmaceutical products tend to be produced from chemically defined raw materials and the manufacture

is controlled using reproducible chemical and physical techniques. Plasma derived medicinal products are inherently variable due to their biological nature, and the biological methods used to test them. Because of the complexity and variability, a high level of expertise is required for the regulation and batch release of these products. As with other biologicals, four principal complementary approaches should be adopted to assure quality and safety:

- *Starting Material:* Assurance of the quality and safety of the plasma for fractionation
- *Manufacturing technique:* Control of fractionation and subsequent manufacturing procedures for isolation, purification, virus removal and inactivation
- *Good Manufacturing Practice (GMP):* Strict adherence to GMP and the prevention of cross contamination
- *Product Compliance:* Standardisation of biological methods needed in the characterisation of in-process and final products.

## **National Medicines Regulatory Authorities: Standards setting**

National MRAs have the duty to ensure that the available pharmaceutical products, whether imported or manufactured locally, are of high quality, safe and efficacious. Plasma derived medicinal products should be included within the legal definition of pharmaceutical products, and fall under the jurisdiction of national MRAs. This function should have a firm statutory and legislative framework.

A national MRA should be an entity fully independent from the manufacturer, undertaking its responsibility in an independent, legal, authoritative and impartial manner.

## **National Medicines Regulatory Authorities: Responsibilities**

### *Regulations*

Individual Member States should develop and institute appropriate national regulations for plasma derived medicinal products. The regulations should take into account specific products, general products, starting materials and be authorised in the respective countries.

They should be based on current international standards, such as those available from WHO and other regulatory authorities. National MRAs should actively participate in initiatives towards international harmonisation of regulation.

### *Documentation*

The national MRA should develop documentation to facilitate the application for registration (market authorisation, licensing) of plasma derived medicinal products.

### *Facility Documentation*

As part of the licensing procedure, details of the manufacturing buildings the location, construction, service facilities and details of the environment should be consolidated in a file (*Site Master File*).

### *Plasma Documentation*

As part of the licensing procedure, for plasma derived medicinal products, information on the collection and control of the starting plasma material, should be documented (*Plasma Master File*).

Such a system aims to ensure quality as well as the traceability of each plasma unit from the donor, through the manufacturing process to the recipient of the product and vice-versa. Documentation should record such information as epidemiological data, the tests performed on the donor, donation, plasma unit, the

plasma pool, and post-pooling information on the manufacture and control of the starting material.

National MRA are responsible for approving the appropriate selection, use and validation of the types of diagnostic tests and test kits used for assaying viral markers. These are used in the testing of blood donations, plasma units and plasma pools prior to entering the fractionation process.

### ***Inspection***

The national MRA has the responsibility to confirm that the manufacturer is adhering to the approved standards of good manufacturing practice and to national and other requirements for the manufacture and quality control of specific products.

### ***Good Manufacturing Practices (GMPs)***

The manufacture of plasma products should be undertaken in accordance with the principles of good manufacturing practices (GMP).

All the steps in their manufacture affect the quality of the final products, therefore all operations should be done in accordance with an appropriate system of quality assurance and current GMP.

### ***Batch Release***

A batch of final product should be homogeneous. Product can be processed in a single process or combine a series of processes.

At the time the product is licensed, the national MRA should decide what level of control is going to apply to demonstrate the consistency of manufacture. The nature of the product and the history of the manufacturer may influence the MRA decision.

### ***Licensing/Marketing Approval***

The national MRA should only issue a license (registration, marketing authorisation) for a specified plasma derived medicinal product when it is satisfied that the

product conforms to the applicable national and/or international requirements, the manufacturer's specifications and has successfully complied with a GMP inspection.

National MRA responsibility includes the approval of viral inactivation and removal procedures applied to the manufacture of plasma derived medicinal products.

### ***International standards***

The measurement of biological activity in human blood plasma products should be directly referenced to the WHO International Standards, defining an internationally agreed unit for a specific activity. Where it exists, the International Unit forms the basis for the establishment of clinical dosing and licensing.

To strengthen harmonisation, the national MRAs should establish appropriate national (*secondary standard*) reference materials calibrated against international reference materials. These can be made available to manufacturers.

### ***Post marketing surveillance***

Countries should establish a national system for the post-marketing surveillance of biological products. Clinicians and other health workers and professionals should be strongly encouraged to report to manufacturers and national MRAs unexpected adverse events occurring after administration of plasma derived medicinal products.

### ***Recall and revocation***

National MRAs should have a system for enforcing the recall of batches, revoking approvals and communicating such decisions to the manufacturer, users and to the MRAs of any countries importing the product.

## References

WHO Requirements for the collection, processing and quality control of blood, blood components and plasma derivatives. WHO Technical Report Series No. 840 (Annex 2)

WHO Guidelines for National Authorities on Quality Assurance for Biological Products WHO Technical Report Series No. 822 (Annex 2)

Regulation and licensing of biological products in countries with newly developing Regulatory Authorities. WHO Technical Report Series No. 858 (Annex 1)

Good Manufacturing Practices for pharmaceutical products. WHO Technical Report Series No. 823 (Annex 1)

Good Manufacturing Practices for biological products. WHO Technical Report Series No. 822 (Annex 1).

*Note: the information in this Fact Sheet does not involve the preparation and scope of application of blood components derived from single donations or small pools, which are used for direct transfusion to patients.*



World Health Organization  
Quality and Safety of Blood Products and Related Substances  
Department of Essential Health Technologies  
20 Avenue Appia, 1211 Geneva 27, Switzerland  
Fax: +41 22 791 4836  
[www.who.int/biologicals](http://www.who.int/biologicals)  
[www.who.int/ehs](http://www.who.int/ehs)