Plasma Protein Therapeutics Association

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PPTA Position Paper on

EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use

Annex 14

Manufacture of Medicinal Products Derived from Human Blood or Plasma

The Plasma Protein Therapeutics Association (PPTA) is the international trade association and standards-setting organization for the world's major collectors of Source Plasma and manufacturers of plasma derived medicinal products and recombinant analogues, collectively referred to as plasma protein therapies. The therapies are used in the treatment of a number of rare diseases. The diseases are often genetic, chronic, life threatening conditions that require patients to receive regular infusions or injections of the therapies for the duration of their lives. The therapies include clotting-factor therapies for individuals with hemophilia A and B and other bleeding disorders; immunoglobulins to treat a complex of diseases in individuals with immune deficiencies; therapies for individuals who have alpha-1 anti-trypsin deficiency, which typically manifests as adult onset emphysema and limits substantially life expectancy; and albumin, which is used in emergency-room settings to treat individuals with shock, trauma, burns, and other conditions. Members are committed to assuring the safety and availability of these medically needed, life-sustaining therapies.

Plasma fractionation is a highly sophisticated manufacturing process that requires dedicated equipment, specific knowledge and long-term experience with the unique starting material for the manufacture of plasma-derived medicinal products, human plasma. There are only a few manufacturers worldwide that can provide this technology, mostly based in the US and in Europe. On the other hand, there are significant amounts of human plasma suitable for manufacture of plasma derived medicinal products available, that are not used, mostly due to regulatory hurdles imposed by countries where manufacturers are located.

It should be an ethical obligation for governments and manufacturers to ensure that as many patients as possible have access to the often life saving therapies manufactured from human plasma. Self sufficiency programs should therefore be encouraged and facilitated by providing established fractionation capacity.

<u>Contract manufacture</u>

Contract manufacturing is a process that establishes a working agreement between two legal entities. As part of the agreement, one company will custom produce parts or other materials on behalf of their customer. Contract fractionation of human plasma from countries with no fractionation capacity is a well established procedure performed by manufacturers of plasma derived medicinal products. There is an abundance of experience and a good safety record of contract manufacture.

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Annex 14

Annex 14 addresses specific provisions when starting material, human plasma, for the manufacture of plasma derived medicinal products is imported from third countries and for contract fractionation programs for third countries.

The adopted version of Annex 14 stipulates in paragraph 2.4 that In the case of third country contract fractionation programs the starting material imported from third countries must be in compliance with the quality and safety requirements as laid down in Directive 2002/98/EC and in Annex V of Directive 2004/33/EC. The activities conducted within the EU/EEA must fully comply with GMP. Consideration should be given to the Community standards and specifications relating to a quality system for blood establishments set out in Commission Directive 2005/62/EC, the traceability requirements and notification of serious adverse reactions and events set out in Commission Directive 2005/61/EC and the relevant WHO guidelines and recommendations as listed in the addendum.

Sources of plasma for contract manufacture:

There are many countries outside the EU, who have no national fractionation facilities for their plasma and must rely on fractionation capacities available at fractionators for example based in the EU to obtain dearly needed plasma protein products for their patients produced from plasma collected in these countries. There are also situations where a manufacturer needs fractionation capacity in addition to their own, because of capacity constraint to manufacture a product not intended for the EU market. There are different scenarios for contract manufacture as part of national self sufficiency programs or as business driven decisions:

1. Countries within the European Union/EEA collect plasma suitable for manufacture into plasma protein therapies and have it fractionated by a manufacturer in another EU/EEA country.
2. Countries outside the European Union that have comparable, but not identical standards for the collection of human blood and plasma in place need fractionation capacity located in the EU.
3. Developing countries complying with the WHO Recommendations for the production, control and regulation of human plasma for fractionation seek contract manufacturing capacity under the WHO Achilles project.

Participants in contract manufacture:

The parties involved in contract fractionation are responsible for the safety of the starting material from their individual perspective. In contrast, the quality of the starting material, the conditions for the manufacture, and the quality and characteristics of the final medicinal products should be restricted to the contractual agreement between the owner of the plasma (the client) and the manufacturer (the service provider).

- Country of origin: The plasma should originate from countries having national regulations for the collection of human blood and plasma in place to protect their donors and recipients of the plasma protein therapies. When contract manufactured plasma derived medicinal products are provided to patients,

suitability of the starting material and quality and efficacy of the final medicinal product needs to be ensured by the National Competent Authority (NCA) of the country of origin of the source material.

- Receiving country: In the EU member State where the contract manufacture is taking place the NCA has the right to ensure that the incoming starting material is of suitable safety. When not in full compliance with EU legislation the relevant provisions of the country of origin of the plasma need to be considered for appropriateness and acceptability in line with the WHO guidelines as stipulated in GMP Annex 14. It cannot be the responsibility of a national competent authority to request that another national competent authority outside the jurisdiction of an overarching legal system such as the European Union fully complies with their rules and regulations. This should also be considered in the context of potential inspections of contributing plasma suppliers by the NCA of the EU member state where the contract manufacture is taking place.
- The service provider: Contract manufacturers of plasma derived medicinal products have to ensure that plasma for fractionation entering their facilities is of appropriate quality and safety, independent of the source or the final destination of the finished product. In Europe, manufacturers strictly adhere to EU requirements pertaining to the manufacturing process for products intended to be marketed within or outside the European Union. Compliance with EU requirements is ensured by inspection and GMP-certification by EU authorities.

Interpretation of the Competent Authorities on Blood and Blood Components

At their meeting on 16 and 17 May 2011 (Summary report Ref. Ares(2011)902136 - 24/08/2011) the Competent Authorities on Blood and Blood Components emphasized that the relevant WHO recommendations are coming close to the EU requirements, and if applied for third country plasma fractionation contracts, would provide good quality and safety for patients in those countries. It was mentioned that it is impossible to enforce EU legislation in third countries and imposing strict criteria may deprive those countries from plasma products. AT Competent Authority noted that imported plasma should be traceable, the blood establishments importing the plasma should have this requirement in the contracts with respective third countries. Furthermore, it was suggested that all products obtained through plasma fractionation should be recorded. Additional operational measures would be needed at national level to trace the flows of products and make sure that residual products are not marketed in EU countries. Following a question from SE Competent Authority, NCAs agreed that in case of third countries fractionation programmes, it is not mandatory for NCAs to inspect blood establishments from third countries, but just to inspect the premises of the manufacturer. When plasma is imported with the purpose of fractionation and marketing of products in EU-countries, the NCAs should also inspect the blood establishments from the country of origin.

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PPTA's interpretation

PPTA agrees with the interpretation of the Competent Authorities on Blood and Blood Components. PPTA interprets the provisions of GMP Annex 14 sections 2.4. and 3.3. that any manufacture of plasma derived medicinal products not intended for EU/EEA markets should be under the supervision of the National Competent Authority of the EU/EEA country where the products are manufactured and notification should be restricted to them. The decision whether inspections of blood/plasma collection establishments by the NCA of the EU/EEA country are necessary should be under the mandate of the two National Competent Authorities involved, i.e. from the non-EU/EEA country where the plasma is sourced and from the EU/EEA country where manufacture takes place. The same principles should apply, when a company manufactures product under its own label intended for non EU/EEA countries.

Conclusion

In conclusion, contract manufacture of plasma derived medicinal products is a well established process to give access to plasma derived medicinal products to the population in the country where the plasma is collected. Regulatory requirements and responsibilities of the involved parties should be carefully balanced to ensure optimal use of the precious starting material, human plasma in the interest of patients in need of these often life saving therapies.