Plasma Protein Therapeutics Association

24 June 2013
Reference: RASC 13010 **By e-mail:** rfs@cofepris.gob.mx

DR: MIKEL ANDONI ARRIOLA PEÑALOSA

Federal Commissioner for Protection against Health Risks
Chairman of National Advisory Committee on Health Regulation and Development

Oklahoma número 14, planta baja

Colonia Napoles, C.P. 03810,

México, D.F.

Subject: PROJECT PROY Standard NOM-257-SSA1-2013, Authorization of medicines registration, renewal and modifications, section 5.7 Blood Products

Dear Dr. ARRIOLA PEÑALOSA,

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, which 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 plasma protein 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. PPTA members are committed to assuring the safety and availability of these medically needed, life-sustaining therapies.

Plasma protein therapies manufactured from human plasma are stable medicinal products with a defined shelf life and distributed globally by PPTA member companies.

PPTA welcomes the proposal to introduce regulations for human plasma for fractionation, the starting material of plasma protein therapies in Mexico as stipulated in PROJECT PROY Standard NOM-257-SSA1-2013, Authorization of medicines registration, renewal and modifications, section 5.7 Blood Products. PPTA would like to take the opportunity to provide our perspectives and experiences pertaining to human plasma for fractionation, which has been successfully established for several years in the European Union (EU) Member States.

We understand that the Mexican proposed Expediente Maestro del Plasma is aimed at regulating the authorization of plasma protein therapies including the starting material, and PROJECT PROY Standard NOM-257-SSA1-2013 aims at incorporating the plasma-related information into the respective product dossier.

Please find below our detailed comments on the proposed regulation Module II. Quality information.

5.7.4.1.

We agree that adherence to high standards for collection of blood and plasma is crucial. We understand that adherence to the standards requested in the European Pharmacopoeia (Ph. Eur.) and/or US Pharmacopoeia (USP) sufficiently ensures the quality of the starting material blood/plasma regarding collection and storage. Request for compliance to requirements exceeding those stipulated in the Ph. Eur and UPS might jeopardize the availability of blood/plasma for products in the Mexican market.

5.7.4.3.1.6 and 5.7.4.3.1.7.

Testing of individual units of plasma for fractionation for *Brucella abortus*, *Plasmodium falciparum* or *Treponema pallidum* is not a requirement by either US or EU authorities for plasma for fractionation. In the US, syphilis testing is part of the ongoing donor suitability testing and not a donation screening. We question the relevance of testing individual units, manufacturing pools or finished product for *B. abortus*, *P. falciparum* or *T. pallidum*, as validated sterile filtration processes are in place in the manufacture of plasma derived products, and also the finished products are tested for sterility. A separate test for either of these pathogens would provide no additional safety assurance or patient protection. To our knowledge, no transmission of brucellosis, malaria or syphilis by plasma derived medicinal products has ever been reported. We would respectfully draw your attention to PPTA's correspondence to the US Food and Drug Administration (FDA) on the subject summarizing the arguments against syphilis testing either routinely on single donations or on manufacturing pools or finished product

(http://www.pptaglobal.org/UserFiles/file/FDAA13013_Syphilis_comments.pdf).

The same arguments are valid for brucellosis or malaria. We would therefore propose to delete these requirements.

5.7.4.3.1.8

We would like to propose to amend the text in this section in the interest of clarity:

"When the starting material is sourced from donors from other countries it must comply with the regulations of the country of origin".

We believe that this text provides sufficient information, because in countries such as the US or the EU Member States, where the majority of the world wide need of human plasma is sourced, there are very detailed provisions for the collection of plasma for fractionation.

5.7.4.3.1.9.

.The provisions of the European Pharmacopoeia for freezing and storage of plasma in a collection center are accepted for PMF certification in the EU. We are aware that Mexico is neither a member nor an observer at the Eur. Ph., but we recommend following a similar approach to regulate freezing and storage and we recommend the following wording:

"When the starting material is sourced from other countries it must comply with the freezing and storage regulations of the country of origin".

5.7.4.3.1.10

For foreign manufactured products, it is requested to comply with both the FEUM and the recognized international pharmacopoeias.

The FEUM monograph on raw materials differs from and partly exceeds the requirements stipulated in reputable international pharmacopoeias like Ph. Eur. or USP, e.g. regarding separation and freezing requirements or testing requirements. We would respectfully like to point out those different or additional requirements, especially exceeding the requirements of Ph. Eur. or USP may lead to a shortage of plasma usable for the manufacture of products for the Mexican market. We understand that up to date compliance with the FEUM monograph on raw materials was not requested for therapies manufactured outside Mexico. It seems prudent to reconsider the

requirements therein and harmonise them with other international Pharmacopoeias such as the USP and the Eur. Ph..

Regarding processing of plasma for the manufacture of coagulation factor products, the FEUM monograph requires separation of plasma from cell components at ≤-30°C during the first 6 hours (or during 18 hours for blood refrigerated between 1-6°C before congelation), which exceeds the requirements of the Eur.Ph. We understand that in general the freezing conditions laid down in the Eur.Ph. sufficiently to ensure preservation of labile proteins, and thus should be accepted also for products for Mexico. Plasma is a limited starting material and it is the commitment of PPTA members or any other manufacturers to use only plasma of the highest quality for the manufacture of plasma derived medicinal products.

We are particularly concerned about the requirement to test for HAV, which is neither required in the US nor in the EU. As stated above the majority of plasma for fractionation is collected in the US and in Europe. The therapies manufactured from this plasma are distributed globally and it is logistically impossible to respect additional and in this case quite onerous requirements in different countries. Such a situation will inevitably lead to impaired access to these often lifesaving medicines in these countries and jeopardises the lives and well-being of patients depending on these therapies.

5.7.4.3.1.11.1.

The validation reports on the freezing conditions are covered by a center's GMP system which is assessed during authority inspections, and validation reports are also verified during establishment audits. Hence such data should not be requested as a part of the documentation on the starting material.

5.7.4.3.1.11.2

In case test kits are commercially available, CE marked or licensed by the FDA, and used according to the manufacturer instructions, validation of the kits has already been assessed by reputable authorities. Thus, for such test kits, a reference to the CE-mark/ US license should be possible instead of provision of validation reports. In case a test kit is not CE marked it should be sufficient to provide a declaration of comparability.

We hope that you will find our comments constructive and useful and remain at your disposal for further discussion. In order to respect the deadline we are submitting our comments in English, but we will submit a Spanish translation within the forthcoming days. We hope that this procedure does not cause any inconvenience.

Yours sincerely,

Dr. Ilka von Hoegen
Senior Director, Quality and Safety