Plasma Protein Therapeutics Association

6 January 2012 **BY Courier**
Reference: RASC12004

Dr. Marcelo Moreira
Agência Nacional de Vigilância Sanitária - ANVISA
Coordenação de Biológicos - CPBIH/GESEF/GGMED

SIA, trecho 5, área especial 57
CEP 71.205-050
Brasília-DF

Brazil

Subject: Resolution RDC No. 55, from December 16, 2010

Dear Dr. Moreira,

The Plasma Protein Therapeutics Association (PPTA) is the international trade association and standards-setting organization for the world's major producers of plasma-derived and recombinant analog therapies. Our members provide 60 percent of the world's needs for Source Plasma and plasma protein therapies. These include clotting therapies for individuals with bleeding disorders, immunoglobulins to treat a complex of diseases in persons with immune deficiencies, therapies for individuals who have alpha-1 anti-trypsin deficiency, which typically manifests as adult onset emphysema and substantially limits life expectancy, and albumin, which is used in emergency room settings to treat individuals with shock, trauma, and burns, among other therapies. PPTA members are committed to assuring the safety and availability of these medically needed life-sustaining therapies for the people who depend on them.

We have taken notice of Resolution RDC No. 55, from December 16, 2010, section III, Production Documentation and Quality Control of Hemoderivatives, VI serological controls.

Before providing you with the scientific rationale supporting a position contrary to the requirements stipulated in the Resolution, we would first like to share with you some operational consequences resulting from the testing requirements of the Resolution. The majority of manufacturers of plasma protein therapies are located in the US and in the European Union. PPTA members only collect plasma in these countries. The plasma collection and manufacture is performed in compliance with US and/or EU regulations. As an observer to the European Pharmacopoeia, you would be aware of Eur. Pharmacopoeial requirements. If a country requests divergent approaches pertaining to plasma for fractionation or manufacture of plasma protein therapies, this would require segregating the starting material, the manufacturing process or the testing procedures from the mainstream operation. Aside from the financial viability of such a labor intensive and costly approach, the available capacities at the manufacturing plant would be a limiting factor. The consequences could be significant shortages of plasma protein therapies in your country, endangering the lives and well-being of Brazilian patients who depend on them.

In addition to operational considerations, we would respectfully like to point out that testing of finished product, either by serology or NAT for HIV, HCV and HBV should not be

required. Available serological or NAT tests are neither intended nor validated for testing of finished products. The combination of NAT and/or serological testing on individual donor units, manufacturing pool level and at least two different validated virus inactivation or virus removal steps build into the manufacturing process are effective measures to ensure the highest margin of safety of plasma protein therapies. This strategy is accepted by regulatory authorities such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). In Europe, serological pool testing for HCV has been replaced by HCV NAT for many years as stipulated in the EMA Guideline on Plasma-Derived Medicinal Products (EMA/CHMP/BWP/706271/2010) and the European Pharmacopoeia Monograph on human plasma for fractionation (853). Furthermore, donation and fractionation pool testing has a higher sensitivity to detect a potential contamination than finished product testing.

For over a decade, PPTA has implemented Voluntary Industry Standards for manufacturing pool testing by NAT for HIV, HCV, and HBV. In 2000 PPTA introduced a Voluntary Industry Standard for Parvovirus B19 requiring that manufacturing pools are tested by NAT to ensure that the pool does not exceed a limit of 10^5 IU/ml.

In view of these measures already in place, testing of finished product does not add to the margin of safety. Matrix effects might lead to false positive results and will cause unnecessary loss of therapies that are frequently in short supply.

Testing of individual units of plasma for fractionation (Source Plasma) for *Treponema pallidum* is not a requirement by either US or European authorities. 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 source plasma units, manufacturing pools or finished product for *T. pallidum*, the causative agent for syphilis as plasma products are sterile, have a validated sterile filtration process in place and the finished products are tested for sterility. A separate test for syphilis would provide no additional safety assurance or patient protection. To our knowledge, no transmission of syphilis by plasma products has ever been reported. Please find attached PPTA's position statement on the subject summarizing the arguments against syphilis testing either routinely on single donations or on manufacturing pools or finished product.

In conclusion, we would respectfully propose adapting Brazilian requirements for plasma protein therapies in accordance with internationally accepted regulations, such as those defined in the European Pharmacopoeia. We interpret your participation as an observer as an indication that you support the Eur. Pharmacopoeial provisions.

In its current form, the Resolution will inevitably have serious consequences to the availability of plasma protein therapies and may endanger the lives of Brazilian patients who depend on these often lifesaving therapies. We do not believe that this is the intention of the resolution.

We hope that you will find our arguments convincing and remain at your disposal for further discussion.

Sincerely Yours,

Dr. Ilka von Hoegen
Senior Director, Quality and Safety

Cc: Dr. Karl-Heinz Buchheit, EDQM

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PPTA Position Statement on Testing of Plasma for Fractionation for *Treponema pallidum*

Treponema pallidum is the cause of syphilis in man. The transmission of syphilis caused by *Treponema pallidum* subspecies *pallidum* via a blood transfusion was first described by Fordyce[1]. Over 200 cases of transfusion-related syphilis have since been published, although over the last 30-40 years post-transfusion syphilis has been reported only sporadically[2]. Testing and questioning of donors has significantly contributed to reducing the number of transmissions by labile blood products. However, according to the EU guideline 2002/98/EC, syphilis testing is not considered a basic testing requirement for whole blood and plasma donations in EU. This position is also reflected in the European Pharmacopoeia monograph on human plasma for fractionation. Furthermore, Directive 2004/33/EC explicitly does not require a deferral period for donors having been cured from syphilis, when the donation is used exclusively for plasma for fractionation. The German Advisory Committee Blood (Arbeitskreis Blut)[3], a committee of the Federal Ministry of Health in Germany, emphasised that testing of plasma regarding syphilis is not considered necessary when plasma is intended solely for fractionation into stable plasma protein therapies.

PPTA member companies collect plasma for the manufacture of plasma protein therapies only in the European Union and the US with a low incidence of syphilis. Testing of blood/plasma for syphilis serves commonly as a surrogate marker for infections caused by other sexually transmitted agents as HIV. Due to the very specific assays currently used to detect HIV, HCV and HBV in blood/plasma donations, testing for syphilis as a surrogate marker for these viruses has no added predictive value[4].

Even if in rare and isolated instances the starting material plasma for fractionation may have an extremely low infectious load this does not pose a safety risk on account of the nature of the manufacturing process. The manufacturing process of plasma protein therapies contains steps capable to inactivate and remove *Treponema pallidum* potentially present in a donation and removes this bacterium completely by the validated sterile filtration of the finished product. Plasma protein therapies can, therefore, not transmit syphilis if manufactured in accordance with GMP because no bacterium would be present in the finished product. In fact, transmission of syphilis by plasma protein therapies has never been reported[5].Testing of single donations or plasma pools for *T. pallidum ssp. pallidum* is therefore not adding to the margin of safety of plasma-derived products.

[1] Fordyce JA: Am J Med Sci 1915;149:781-808
[2] Wendel S. Vox Sang 1994; 67 (suppl 3): 161-174
[3] Arbeitskreis Blut. Transfus Med Hemother 2005;32:174-183
[4] Zou et al., Transfusion 2009;49:655-661
[5] Commentary on Ph. Eur. 5.0 22 lfg 2005

Boulevard Brand Whitlock, 114/5 · 1200 Brussels BELGIUM · tel : +32.2.705.58.11 · fax : +32.2.705.58.20
VAT: BE453 837 462 · e-mail: pptaeu@pptaglobal.be · www.pptaglobal.org
PPTA Offices in Brussels · Washington · Annapolis · Tokyo